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FRIEDREICH'S ATAXIA AND ITS CARDIAC MANIFESTATIONS

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FRIEDREICH'S ataxia is a chronic, progressive, heredodegenerative disease which has its onset in early life. Its association with cardiac disease and manifestations were first noted by Friedreich,[1] who originally described the syndrome. The accumulative clinicopathologic reports in the French, English, and recently, the American literature are adding to the information by which, we hope, some day to discover its etiology and therapy.

The pathology of this disease shows neurologic degenerative processes involving the posterior and lateral columns of the spinal cord, the fasciculus gracilis and cuneatus, the spinocerebellar tracts, and Clarke's columns. Lesions of the dorsal root and posterior columns are most severe in the lumbosacral region with an ascending degeneration. Occasionally the medulla oblongata and cerebellum are involved. In a few reported cases there was atrophy of the anterior horn cells with degenerative changes in the peripheral nerves and the posterior roots. Marked proliferation of glia fibers are seen in the degenerated fiber tracts.

NEUROLOGIC SYMPTOMS

The neurologic symptoms are as follows: (1) ataxia—individual walks on a "broad base," gait is "drunken"; (2) ataxic speech—slow, unclear, dysarthritic, scanning, syllabilization, explosive; (3) mentality usually intact, though it may be somewhat retarded; (4) scoliosis; (5) pes equinovarus with arching of foot, cavus and hyperextension of the large toe; (6) deep tendon reflexes, diminished to absent; (7) Babinski's sign usually positive; (8) Romberg's sign usually positive; (9) nystagmus may be present, and (10) impairment of position and vibratory sense.

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PATHOLOGY

In the pathology of the heart the following picture was almost invariably present: (1) cardiac hypertrophy involving all chambers of the heart, especially the left ventricle, (2) diffuse interstitial fibrosis of the myocardium, (3) fatty degeneration of the myocardium, (4) round cell infiltration with lymphocytes and eosinophils, (5) endocardium and valves, normal, and (6) coronary arteries varying from normal appearance to diffuse atheromatous involvement with or without obstruction.

In the pathology of the heart the following picture was occasionally seen: (1) pericardial effusion (three cases), (2) complete heart block, bundle branch block, (3) infiltration with mast cells, neutrophilic leukocytes, (4) cardiac dilitation, (5) epicardial petechiae and hemorrhages, and (6) fibrous pericardial thickening.

In the microscopic study of the heart the average case revealed: (1) collagenous tissue replacement of degenerating myocardium with compensatory hypertrophy of remaining muscle fibers, (2) nuclei of muscle fibers large, vacuolated, and hyperchromatic, (3) cross striations usually absent, (4) Purkinje fibers of node and conducting system similarly separated by fibrous tissue and a sparse cellular infiltration, (5) longitudinal fibrils occupying peripheral sarcoplasm, granular cytoplasm in center of cell, presence of lipochrome pigment, and (6) destruction of muscle by focal coagulation necrosis of its fibers.

In the pathology of the liver the following picture was depicted: (1) chronic passive congestion, (2) edema, and (3) fatty degeneration.

In the spleen there was chronic passive congestion.

In the lungs there was the following: (1) pulmonary congestion and edema, and (2) pleural effusion.

In the adrenals one case had a single cortical adenoma in an otherwise normal adrenal gland.

CARDIAC FINDINGS

The signs and symptomatology of the cases vary with the heart size, that is, whether the heart is normal in size as seen in many cases or hypertrophied and dilated.

The symptoms are as follows: (1) congestive failure, (2) palpitations, (3) substernal and retrosternal oppression and pain, (4) anginal syndrome, and (5) acute myocardial infarction (one case).

The signs are as follows: (1) systolic precordial murmur, (2) early and mid-diastolic apical murmur with accentuated P_2 (confirmed by phonocardiogram), (3) presystolic apical murmur heard best after exercise (confirmed by phonocardiogram), (4) diastolic apical murmur associated with auricular fibrillation present in several cases (necropsy revealing an absence of valvular lesions and microscopic evidence of rheumatic involvement of the myocardium), (5) paroxysmal bouts of auricular tachycardia, (6) auricular fibrillation, (7) regular sinus rhythm with numerous auricular premature contractions or ventricular premature contractions, and (8) parasystolic ventricular rhythm (one case).

COMMENT

The two factors which most commonly cause fatty degeneration are the action of toxins and the lack of oxygen. The bacterial toxins are organic poisons, and fatty degeneration as seen frequently in acute or chronic infections. Phosphorus, chloroform, and alcohol are the most common inorganic poisons which may result in fatty degenerations. Pernicious and secondary anemias are both causes of insufficient oxygenation, which may lead to fatty degeneration. It would be interesting to note whether the neutral fats (esters of triatomic alcohol glycerin and a fatty acid) or the lipoids (namely, cholesterol and cholesterol ester) are affected. Investigation along these lines may bring forth some interesting results. Focal coagulation necrosis of the cardiac musculature may be an additional point to be stressed in the determination of the etiology. It is usually seen following infarction, with a resultant coagulation of the cytoplasm by intracellular enzymes.

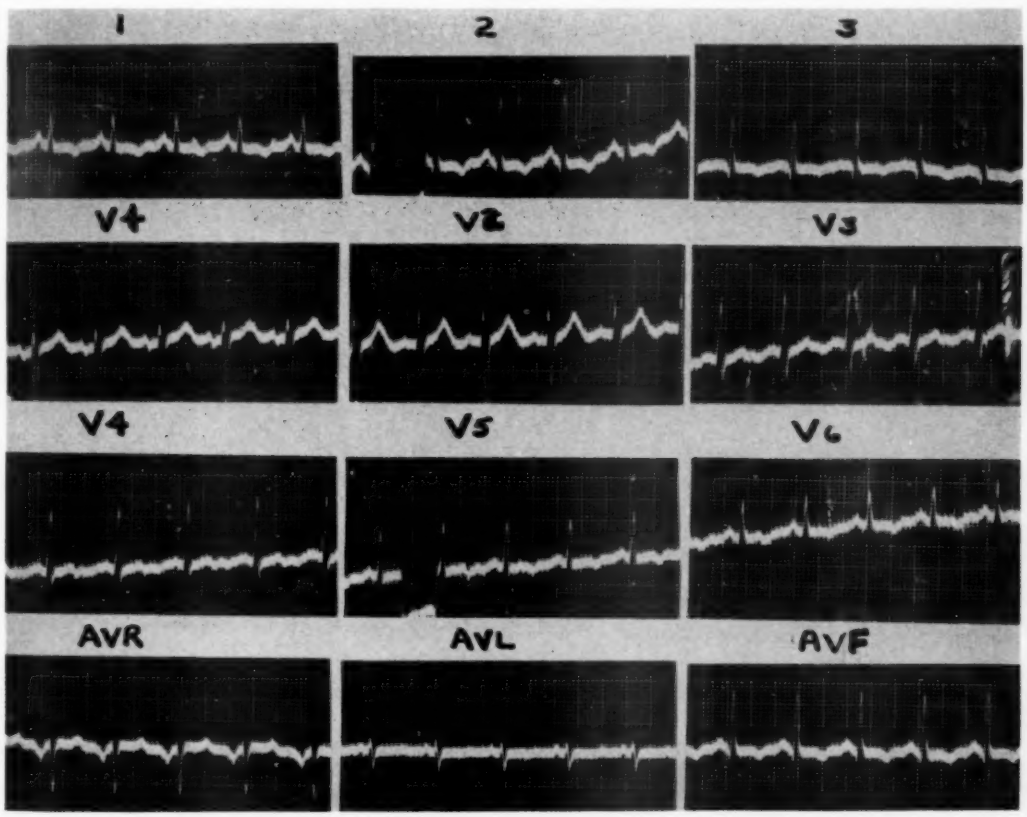

Fig. 1 (A. S.).—Regular sinus rhythm. No axis deviation. Inverted $T_1T_2T_3$. Inverted T in V_4, V_5, and V_6. In aV_R, small R, upright T. In aV_F, inverted T.

RESUME OF FINDINGS IN ELEVEN CASES

There were eight men and three women patients, all Caucasian. Their ages at that time varied from 27 to 66 years in the women, and 36 to 45 years in the men. Our series included a brother and two sisters who had Friedreich's ataxia. Familial involvement was present in six

of the nine cases. The average age at onset was 14 years, youngest at 5 years, and the oldest at 24 years. The essential neurologic symptoms for the diagnosis of Friedreich's ataxia were present in all cases, with occasional negative findings of nystagmus, scanning speech, and signs of mental retardation or disturbance. Two cases evidenced congestive failure; one had paroxysmal auricular tachycardia, and another had paroxysmal auricular fibrillation. Eight cases of the eleven lacked cardiac symptoms. The heart was enlarged in only three cases. Murmurs were not present in eight of the eleven patients. The presence of a presystolic apical murmur followed by early systolic and protodiastolic murmurs, in addition to bouts of paroxysmal auricular tachycardia, lead us to suspect rheumatic carditis with mitral stenosis and insufficiency in one case. (This will be discussed later.) Premature contractions appeared in only two patients, one being premature auricular contractions and the other, premature ventricular contractions. All of these patients had negative Wassermann reactions. There were two deaths in this series, one of bronchopneumonia and the other of congestive heart failure.

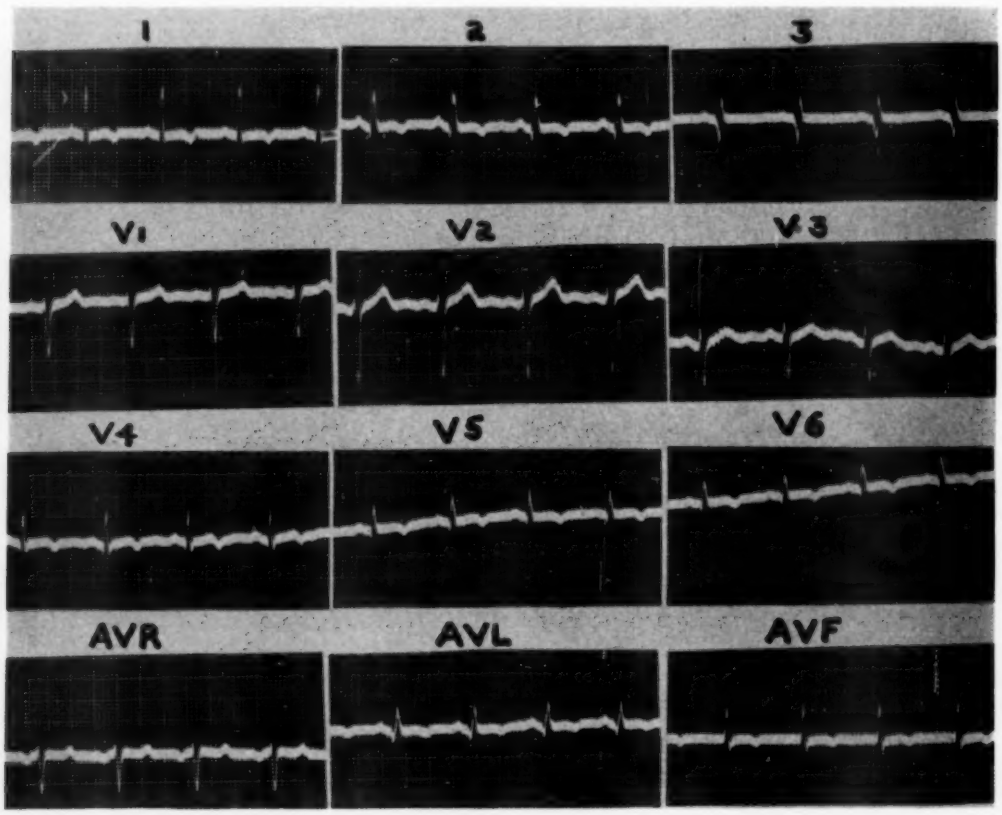

Fig. 2 (S. S.).—Regular sinus rhythm. Inverted $T_2T_3Q_3$. Clockwise rotation. Inverted T_6. In aV_R, small R, upright T. In aV_L, isoelectric T. In aV_F, inverted T.

ELECTROCARDIOGRAPHIC INTERPRETATIONS

There was clockwise rotation in six cases; counterclockwise rotation in one case, and low voltage in three cases. The most significant and persistent findings were as follows: In the standard leads: Lead I showed negative or isoelectric T in seven cases, three of which showed a small Q wave. Lead II showed negative or isoelectric T in nine cases, four of whice showed a small Q wave. Lead III showed an inverted to isoelectric T in eight cases, seven of which showed a small Q wave. In the precordial or V leads two cases had inverted T waves from V_1 to V_6. Two

cases showed inverted T waves from V_2 to V_6; one case showed inverted T waves from V_3 to V_6; two cases showed inverted T waves from V_4 to V_6; one case showed inverted T waves in V_6, and one case showed inverted T waves in CF_4. In two cases the tracing was within normal limits.

In the unipolar or aV leads the following electrocardiographic findings were recorded: aV_R showed presence of an R wave in six cases; an upright T in seven cases, an isoelectric T in one case, and second T was normal in one case. aV_L showed the following: Small R, small S in two cases; small R, deep S in one case; small R in one case, moderate to tall R in four cases; small Q in two cases, sagging S-T in two cases; negative T in five cases, isoelectric T in three cases, and diphasic T in one case. aV_F showed the following: Small R in two cases; moderate R, small S in one case; moderate to high R in two cases; small Q in three cases; small Q, small R in one case; small Q, deeper S in one case; splintered QRS in one case; sagging S-T in two cases; negative T in six cases; isoelectric T in one case, and diphasic T in one case.

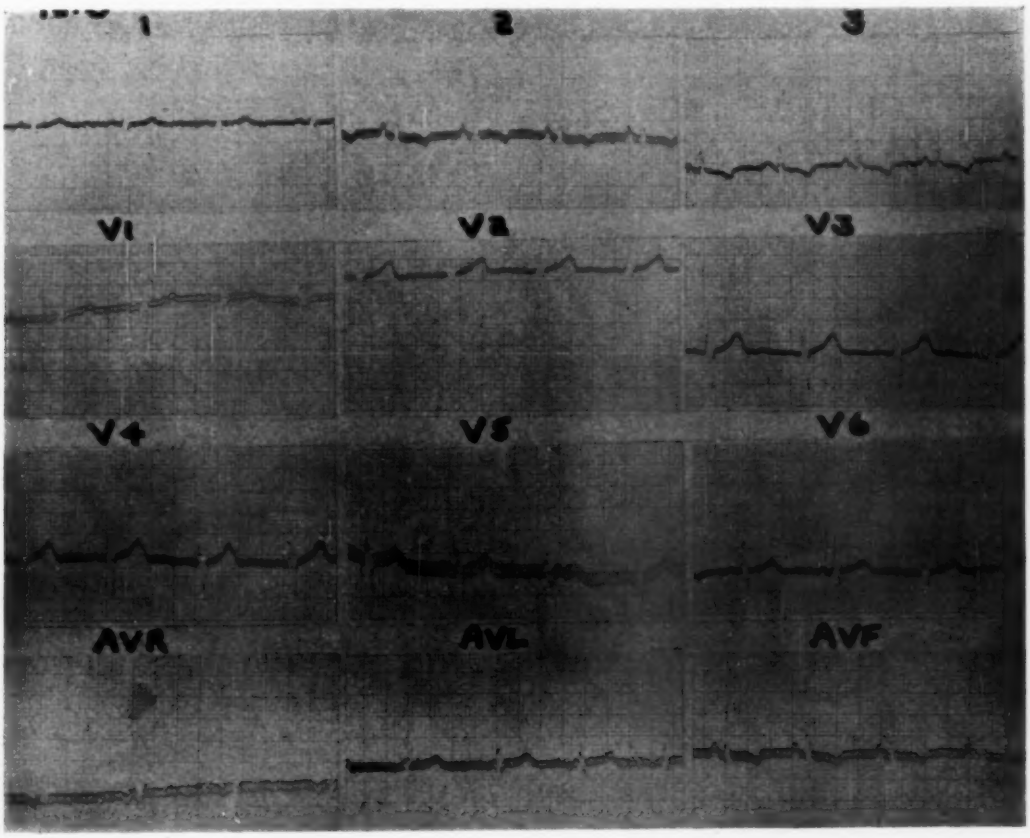

Fig. 3 (N. S.).—Regular sinus rhythm. Inverted T_2T_3. Clockwise rotation. In aV_F, inverted T.

AUTOPSY OF REPORTED CASE

R. M. expired at the age of 29 years. Patient was psychotic. Other than Friedreich's ataxia, the only pertinent history is that of a questionable rheumatic fever and carditis at the age of 10 years. (See Table I for additional information.)

Autopsy report showed: degeneration of the posterior column, crossed and direct pyramidal, and anterior spinocerebellar tracts; diffuse chronic interstitial myocarditis; chronic passive congestion of liver and spleen; congestion and edema of lungs; mural thrombus in auricular appendage;

thrombi in splenic arteries; infarct of spleen; infarct of kidney; bilateral lobular pneumonia; degeneration of peripheral nerves; atrophy of skeletal muscles; kyphoscoliosis; bilateral pes cavus; congenital anomaly aberrant persistent thymus tissue, and chromophobe adenoma of pituitary.

A section of the ventricle revealed a diffuse interstitial eosinophilic material in which a few lymphocytes and fibroblasts were seen, also marked hypertrophy of the muscle fibers. The hypertrophy and interstitial fibrosis was diffuse and uniform throughout the section. In trichrome stains, the interstitial material was green. Some of the large muscle fibers were vacuolated. A section of the auricle showed a mural thrombus with partial organization and a similar condition of hypertrophy and interstitial fibrosis.

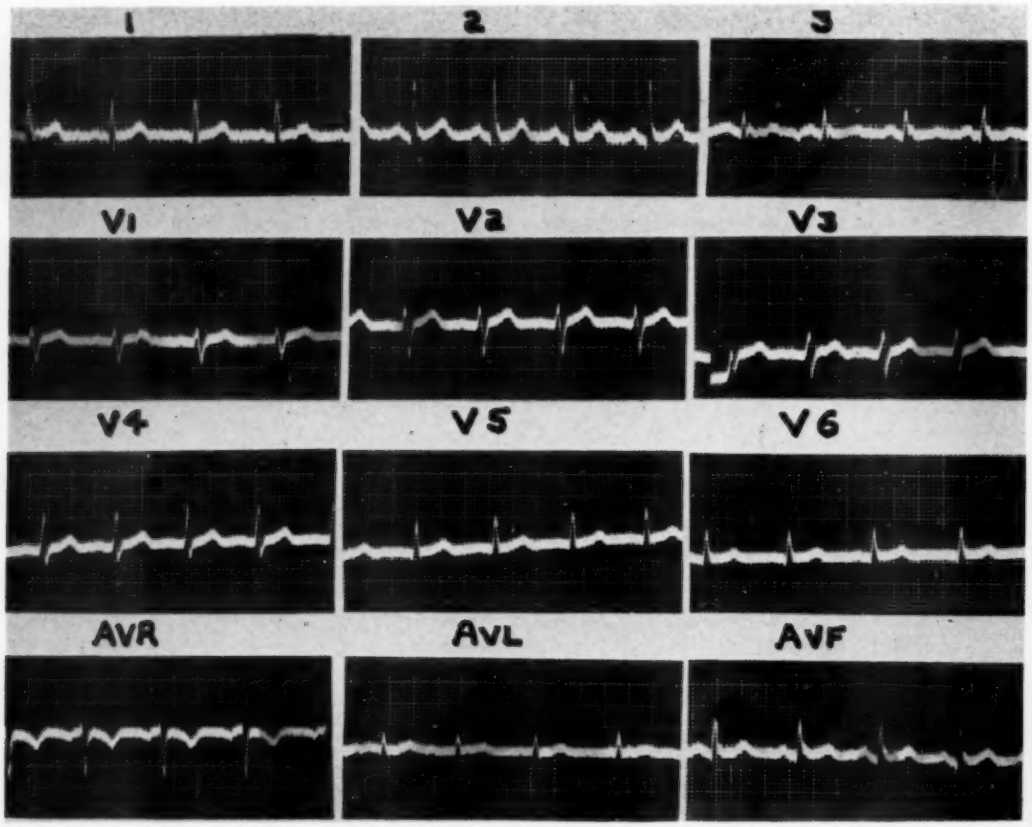

Fig. 4 (L. C.).—Regular sinus rhythm. Notched QRS in Lead III.

The gross and microscopic picture of the heart included all of the pathologic processes almost invariably seen (noted in pathology at start of paper) in previous cases of Friedreich's ataxia. Of interest is the presence of aberrant persistent thymus tissue, and a chromophobe adenoma of the pituitary. The latter two findings were never noted in previous autopsy reports of cases of Friedreich's ataxia. They may be incidental findings, but should be sought for in future autopsies in cases of this kind.

The course is progressive in character. The disease may last from thirty to forty years. The patient may become bedridden at any time during the progression of the disease. The lower extremities are usually involved prior to the upper extremities. The patient may die of congestive failure or an intercurrent infection, such as pneumonia.

To date the therapy is symptomatic. Passive and active exercises are of little avail.

DISCUSSION

Friedreich, in 1863, was the first to describe this rare familial disease resulting from degeneration of the posterior columns, spinocerebellar tracts, and the cells of Clarke's columns. He reviewed six cases, five of which presented cardiac abnormalities. On post-mortem examination of three cases, two revealed fatty degeneration of the myocardium. One case had diffuse cardiac hypertrophy with valvular disease (aortic and mitral) which was suggestive of rheumatic involvement. There was also fatty degeneration of the liver. Pitt, in 1887,[2]

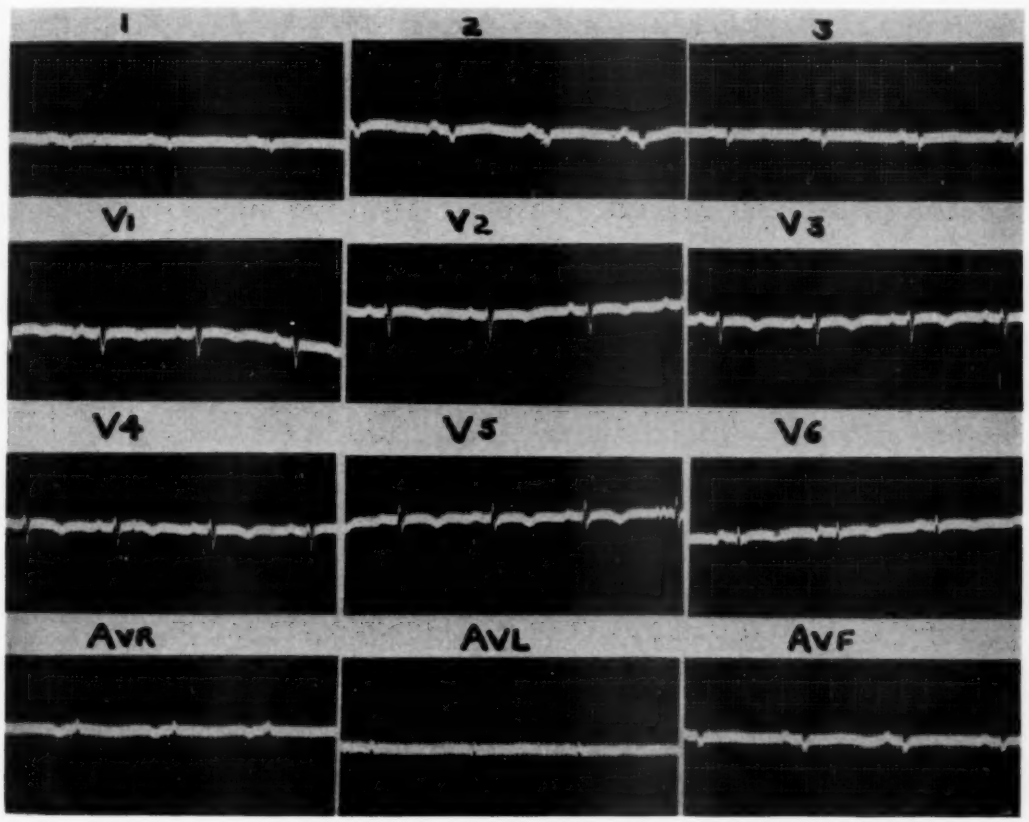

Fig. 5 (E. B.).—Regular sinus rhythm. Low voltage; isoelectric T_1T_2; low T_3. Q_2. Clockwise rotation. Low voltage in V leads. Inverted T in V_1-V_6. Low voltage in aV leads. In aV_R, R is present, flat T. In aV_L, inverted T. In aV_F, splintered QRS, flat T.

stressed the presence of deranged cardiovascular function and cardiovascular manifestations in patients with Friedreich's ataxia. Necropsy findings in his case revealed diffuse interstitial myocardial fibrosis and round cell infiltration. The cusps of the aortic valve were adherent and their margins were irregular and calcareous.

TABLE I.

PATIENT	SEX	AGE (YRS.)	FAMILIAL INVOLVEMENT	ASSOCIATED DISEASES	AGE AT ONSET (YRS.)	ATAXIA	SPEECH SCANNING	MENTALITY	SCOLIOSIS	PES EQUINO-VARUS (CAVUS)	DEEP TENDON REFLEXES*	SIGNS		NYSTAGMUS	LOSS OF POSITION AND VIBRATORY SENSE
												BABINSKI	ROMBERG		
A. S.	F	39	Sister (N.S.) and brother (S.S.) One brother living and well Negative maternal and paternal history	RHD?	19	+	+	N	+	+	+	+	+	−	+
S. S.	M	36	(See Patient A. S.)	None	19	+	−	N	+	+	+	+	+	−	+
N. S.	F	38	(See Patient A. S.)	Renal calculi	24	+	−	N	+	+	+	+	+	−	+
L. C.	M	45	One of six children One brother has F.A. (onset at 15 yrs.) One brother has unilateral pes cavus	Peptic ulcer	14	+	+	N	+	+	+	+	+	+	+
E. B.	F	48	One brother has F.A. (onset at 9 yrs.)	None	9	+	+	N	+	+	+	+	+	+	+
M. F.	F	66	None	Rheumatoid arthritis Cystitis Blepharitis Cerebral thrombosis Broncho-pneumonia	18	+	+	+	+	+	+	+	+	−	+
A. E.	F	42	One brother had F.A. (onset at 8 yrs.)	Psychosis Suicidal	14	+	+	+	+	+	+	+	+	+	+

				pneumonia											
A. E.	F	42	One brother had F.A. (onset at 8 yrs.)	Psychosis Suicidal tendencies Optic atrophy Bilateral nerve deafness Hypertension	14	+	+	+	+	+	+	+	+	+	+
M. M.	F	46	None	Bilateral nerve deafness	14	+	+	+	+	+	+	+	+	+	+
O. N.	F	29	None	Nonspecific vaginitis	5	+	+	+	+	+	+	+	+	+	+
R. C.	F	44	One sister has F.A.	Chorea at 10 yrs. Broncho-pneumonia (cause of death at 44 yrs.)	10	+	−	N	+	+	+	+	+	−	+
R. M.	F	27	One brother had F.A. (onset at 15 yrs.) Died of "heart trouble." Mother's cousin had F.A.	Questionable rheumatic fever and carditis at 10 yrs. Psychosis	12	+	+	+	+	+	+	+	+	+	+

*Deep tendon reflexes absent to deficient.

Key:

F.A., Friedreich's ataxia
RHD, Rheumatic heart disease
RSR, Regular sinus rhythm
VPC, Ventricular premature contractions
N, Normal
APC, Auricular premature contractions

TABLE I—CONT'D

PATIENT	SEX	AGE (YRS.)	CARDIAC SYMPTOMS	HEART SIZE	MURMURS	RHYTHM	STANDARD LEADS			PRECORDIAL LEADS						UNIPOLAR LEADS		
							I	II	III	V_1	V_2	V_3	V_4	V_5	V_6	aV_R	aV_L	aV_F
A. S.	F	39	Palpitation, Paroxysmal auricular tachycardia Congestive failure	Enlarged	Presystolic apical murmur, early systolic murmur, and protodiastolic murmur. Confirmed by phonocardiograph	RSR	Prominent P T↓	Prominent P T↓	T↓	N	N	N	T↓	T↓	T↓	Small R T↑	Small R Deep S T_{iso}	Tiny Q Tall R T↓
S. S.	M	36	None	Within normal limits	None	RSR	N	Tiny Q T↓	Deep Q T↓	Clockwise rotation Persistence of S in V_1 to V_6					T↓	Small R T↑	Tall R T_{iso}	Small Q T↓
N. S.	F	38	None	Within normal limits	None	RSR	N	T↓	T↓	Clockwise rotation. Persistence of S in V_1 to V_6 Otherwise in normal limits						N	Small R Small S	Tall R T↓
L. C.	M	45	None	Within normal limits	None	RSR	N	Tiny Q	Tiny Q Notched QRS	N	N	N	N	N	N	Small R	N	Tiny Q
E. B.	F	48	Congestive failure	Enlarged	None	RSR with occasional VPC's	Low voltage Tiny Q T_{iso}	Mod. Q Splint. QRS T_{iso}	Tiny Q Deep S Low T	Clockwise rotation Persistence of S in V_1 to V_2 Low voltage T↓	T↓	T↓	T↓	T↓	T↓	Absent Q R wave Flat T	Low voltage Tiny Q Tiny R T↓	Tiny Q Deeper S Splint. QRS T flat
M. F.	F	66	None	Within normal	Soft systolic murmur over	RSR	T↓	T_{iso}	Mod. Q T↑	N	N	T↓	T↓	T↓	T↓	T↑	Tall R	Small R

M. F.	F	66	None	Within normal limits	Soft systolic murmur over aortic and pulmonic areas	RSR	T ↓	T_{iso}	Mod. Q T ↑	N	N	T ↓	T ↓	T ↓	T ↓	T ↑	Tall R T ↓	Small R T ↑
A. E.	F	42	None	Within normal limits	None	RSR with multiple APC's	Tiny Q T ↓	T ↓	Tiny S T ↓	Clockwise rotation Persistence of S in V_1 to V_5 N	T ↓	T ↓	T ↓	T ↓	T ↓	Small R T ↑	Small R Tiny S T_{iso}	Mod. R Tiny S T ↓
M. M.	F	46	None	Enlarged	Rough systolic murmur at left second intercostal space	RSR	T ↓	T ↓	Small R Deep S T ↓	Counterclockwise rotation Tall R in V_2 with small S N	T ↓	T ↓	T ↓	T ↓	T ↓	T ↑	Mod. R T ↓	Small R T ↓
O. N.	F	29	None	Within normal limits	None	RSR	Mod. QS ∓T	Sag. S-T T ↓	Tiny Q T ↓	Clockwise rotation Persistence of S in V_1 to V_6 Low voltage T_{iso}	T ↓	T ↓	T ↓	T ↓	T ↓	Small R T ↑	Small R Deep S T_{iso}	Tiny Q Sag. S-T T ↓
R. C.	F	44	None	Within normal limits	None	RSR	∓T	T ↓	T_{iso}	CF_4 only Sagging S-T T ↓								
R. M.	F	27	Paroxysmal auricular fibrillation	Within normal limits	None	RSR Auricular fibrillation	Small R Deep S	Prom. P	Slur. upstroke QRS Tiny Q ∓T	Clockwise rotation Persistence of S in V_1 to V_6 N	N	N	T ↓	T ↓	T ↓	Tiny R Small S High R′ T ↑	Tiny R Deep S T ↓	Moderate R Sag. S-T ∓T

*Prom., Prominent
Mod., Moderate
Splint., Splintered
Sag., Sagging
Slur., Slurring

Loiseau,[9] in 1938, collected and reviewed the literature. He believed in the theory of degeneration of the vagal nuclei with resultant sympathetic hypertonia. His series collected from literature included sixteen autopsied cases, three of which were excluded because of valvular lesions, six who had hypertrophy of heart, and four had dilitation. Fatty degeneration was found in six; one heart was described as small, others were normal.

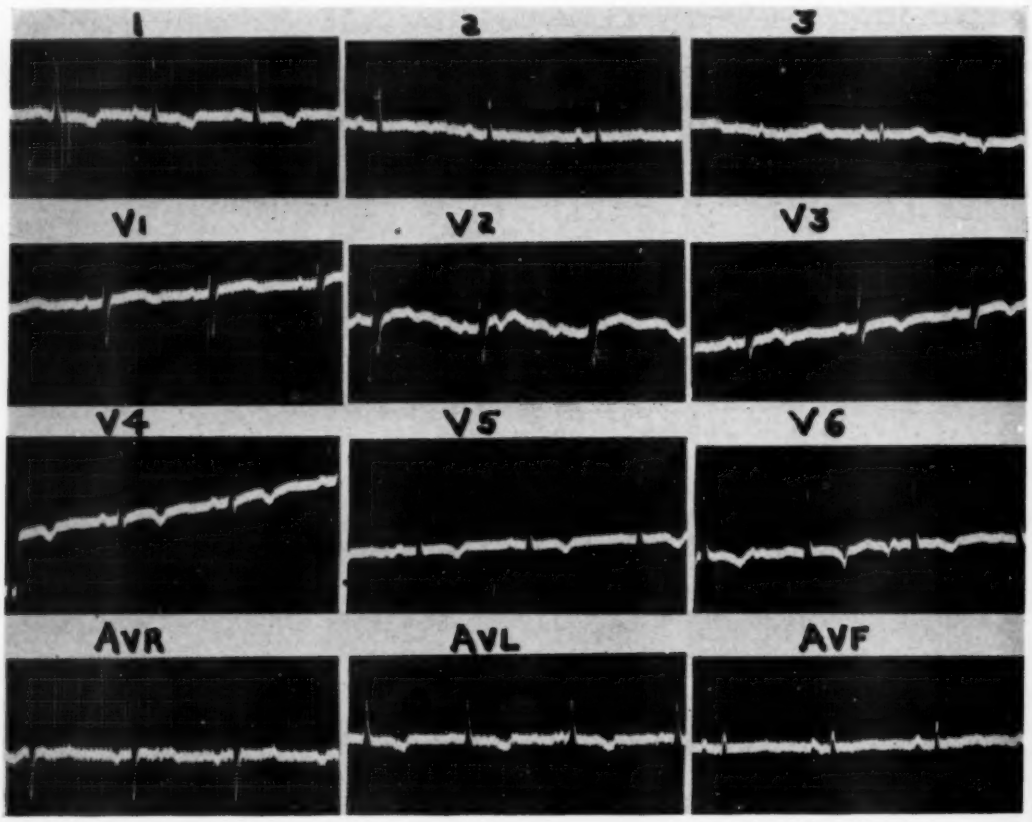

Fig. 6 (M. F.).—Regular sinus rhythm. Inverted T_1. Isoelectric T_2. Inverted T in V_2-V_6. In aV_R, upright T. In aV_L, inverted T.

Russell,[12] in 1946, reviewed four autopsied cases of Friedreich's ataxia, three of whom had heart failure with associated chronic myocarditis. The fourth patient expired within twenty-four hours after admission to the hospital. Hypertrophy of the heart, diffuse interstitial myocardial fibrosis, fatty degeneration of myocardial fibers, and normal valves and endocardium were present in all four cases. One case revealed diffuse atheromatous involvement of the coronary arteries; in another the involvement was slight, and in another the coronary arteries appeared normal. No mention of the coronary arteries was made in her first case. Congestion and fatty degeneration of the liver and kidneys were noted in three cases. Russell proposed the "toxin" theory as the probable etiology of the neurologic and cardiac manifestations. She did not find any significant changes involving the vagal nuclei.

Van Bogaert and Van Bogaert,[7] in 1936, found evidence of myocardial damage in four of eight cases. Two patients had inversions of T_1T_2, and two cases revealed negative T waves in T_2T_3.

Evans and Wright,[10] in 1942, described thirty-three cases of Friedreich's ataxia which had electrocardiographic studies. Twelve showed definite and significant changes which consisted of coronary type T waves in Leads I or III, low voltage of T waves, or bundle branch block. An additional ten cases revealed slight abnormalities as evidenced by deep slurred S waves. The incidence of electrocardiographic changes did not appear to be related to sex, age, or time of onset of Friedreich's ataxia. The authors noted that affected members of the same family tended to show identical electrocardiographic changes.

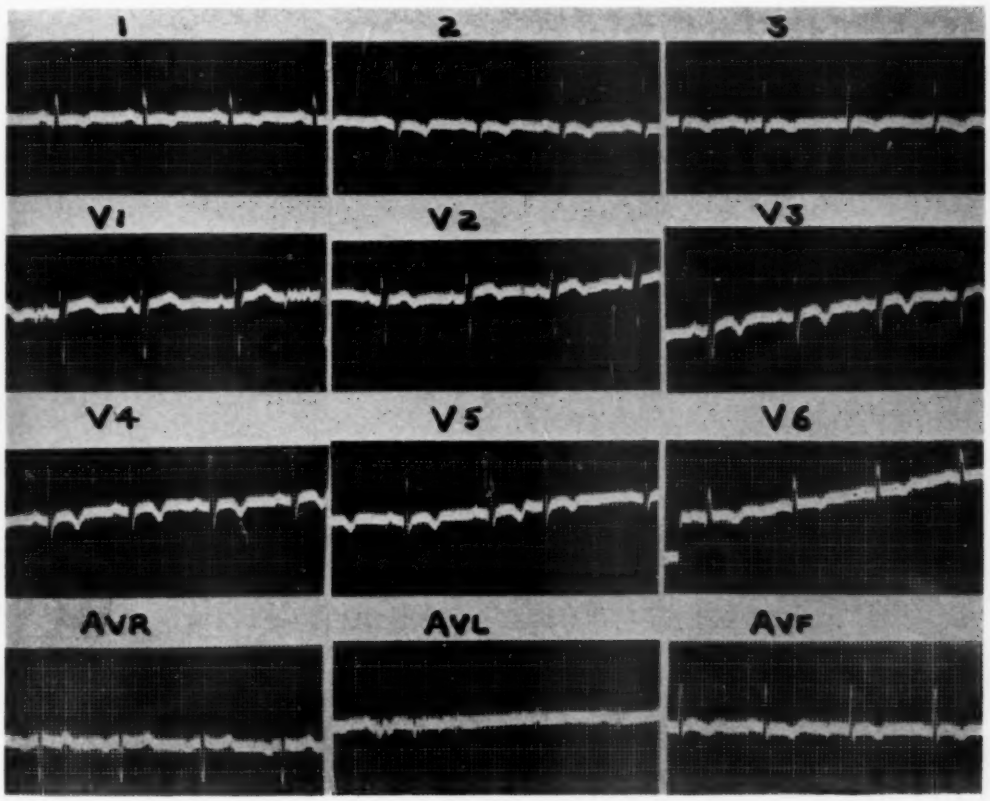

Fig. 7 (A. E.).—Regular sinus rhythm with auricular premature contractions. Inverted $T_1T_2T_3$. Clockwise rotation. Inverted T in V_2-V_6. In aV_R, small R, upright T. In aV_L, isoelectric T. In aV_F, inverted T.

Piron,[11] in 1946, suggested that the electrocardiographic abnormalities represented coronaritis visualized by depression of the S-T segment or inversion of T_1T_2 or a deep Q_3 with negative T_3. The electric axis usually showed a right axis deviation. He reviewed two cases, stating that the electrocardiographic alterations corresponded to coronary insufficiency. His theory linking cardiac lesions to medullary lesions was stated in the etiology.

Ellwood,[13] in 1948, described two cases of Friedreich's ataxia, in which both patients had bouts of paroxysmal auricular tachycardia. Autopsies were performed on both cases. The first case had pulmonary congestion and edema, hypertrophy of both ventricles, scarring and thickening of the mitral valve, and a thrombus at the bifurcation of the left coronary artery. The second case also had pulmonary edema, in addition to pericardial effusion, cardiac hypertrophy, diffuse interstitial myocardial fibrosis, atelectasis, and a purulent lobular pneumonia. The valves, aorta, and coronary arteries were normal.

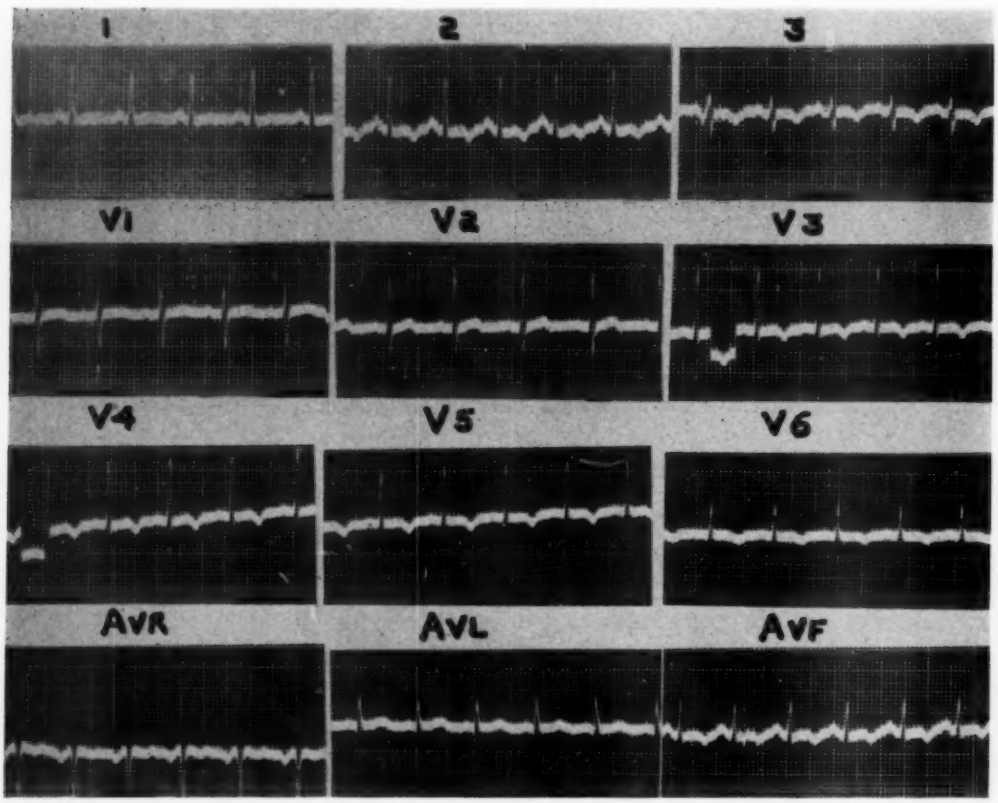

Fig. 8 (M. M.).—Regular sinus rhythm. Inverted $T_1T_2T_3$. Counterclockwise rotation. Inverted T in V_2-V_6. In aV_R, upright T. In aV_L and aV_F, inverted T.

Hejtmancik, Bradfield, and Miller,[14] in 1949, reported two cases; autopsy was performed on one. In the first case palpitations and paroxysmal auricular fibrillation were apparent. Clinically the heart was enlarged, and protodiastolic and mid-diastolic murmurs were heard at the apex. The murmurs were confirmed by phonocardiograms. Electrocardiogram revealed RST, supraventricular ectopic beats, deep Q_1Q_2, flat T_1, and negative T_2T_3. Necropsy revealed an enlarged heart, hypertrophy and dilitation of both ventricles, diffuse interstitial myocardial fibrosis with compensatory hypertrophy of remaining fibers, round cell infiltration, pulmonary edema, and congestion of the liver. The valves and

coronary arteries were normal. In the second case, heart borders were within normal limits and regular sinus rhythm with occasional premature contractions. Upon exercise with a resultant tachycardia, a short low-pitched presystolic murmur was heard at the apex, confirmed by phonocardiogram. Electrocardiogram revealed regular sinus rhythm, frequent auricular premature contractions, tiny Q in first lead and in aV_F; $T_1T_2T_3$ were inverted, RS-T segments were elevated in Leads CF_2 and IV F. Rheumatic heart disease with mitral stenosis was suspected in the first case, but not confirmed at necropsy.

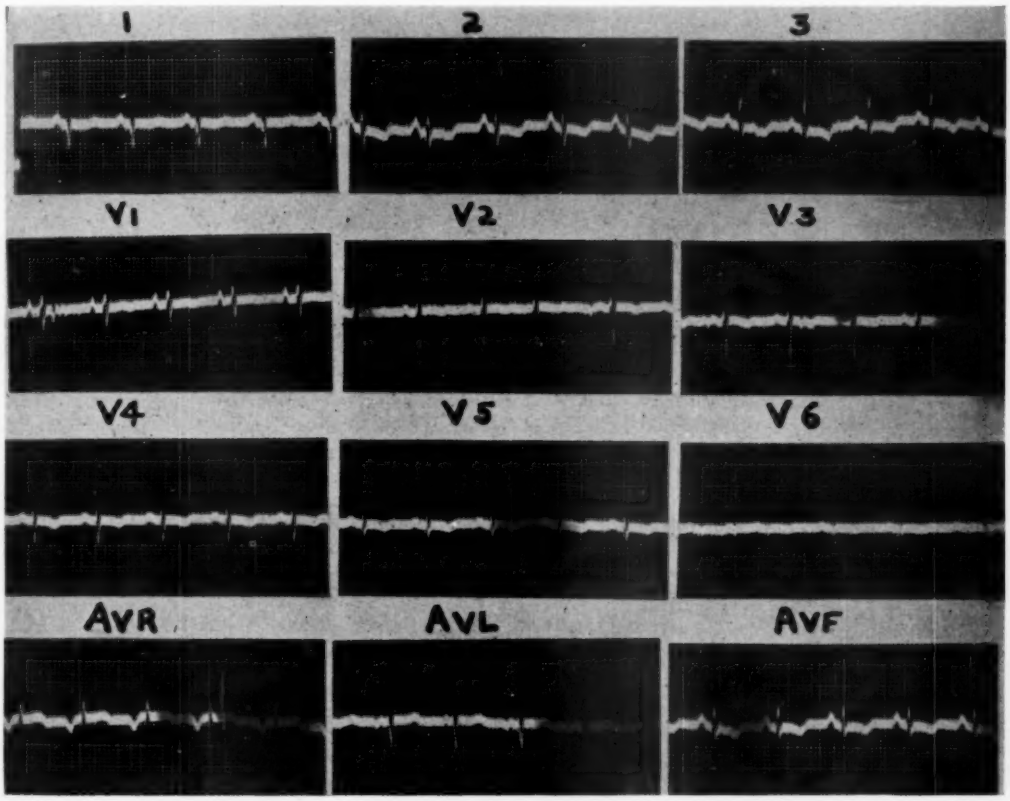

Fig. 9 (O. N.).—Regular sinus rhythm. In Lead I, ∓ T. In Lead II, sagging S-T, inverted T. In Lead III, inverted T. Clockwise rotation. Isoelectric T in V_1. Inverted T in V_2-V_6. In aV_R, small R, upright T. In aV_L, isoelectric T. In aV_F, sagging S-T, inverted T.

Isolated cases with electrocardiogram abnormalities have been reported in the French literature.

Nadas, Alimurung, and Sieracki[15] presented six cases of Friedreich's ataxia with cardiac changes. The first case had an enlarged heart and a systolic murmur over the left second intercostal space. The patient developed pneumonia and expired. Autopsy revealed a diffuse interstitial myocardial fibrosis, fatty degeneration of the cardiac musculature, atheroma with varying degrees of obstruction of the coronary arteries, and pulmonary congestion, edema, and bronchopneumonia.

Electrocardiograms taken on the other five patients revealed inverted T waves in the standard leads and depressed S-T segments in Leads I and II. In the precordial leads, the T waves were diphasic to inverted from V_4 to V_6, and in one case, from V_1 to V_6. A depressed S-T segment was seen in V_6. In the aV_F lead, tall R and inverted T was the usual picture. Heart enlargement was noted in three of the six cases. Murmurs were noted in the left second intercostal space in two cases; apical systolic in two cases, and two Grade III pulmonic systolic murmurs.

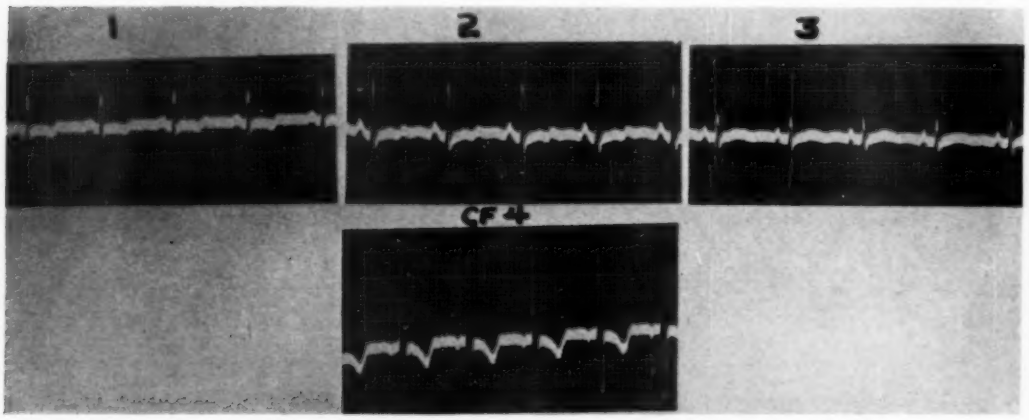

Fig. 10 (R. C.).—Regular sinus rhythm. In Lead I, ∓ T. In Lead II, inverted T. In Lead III, isoelectric T. In CF_4, sagging S-T, inverted T.

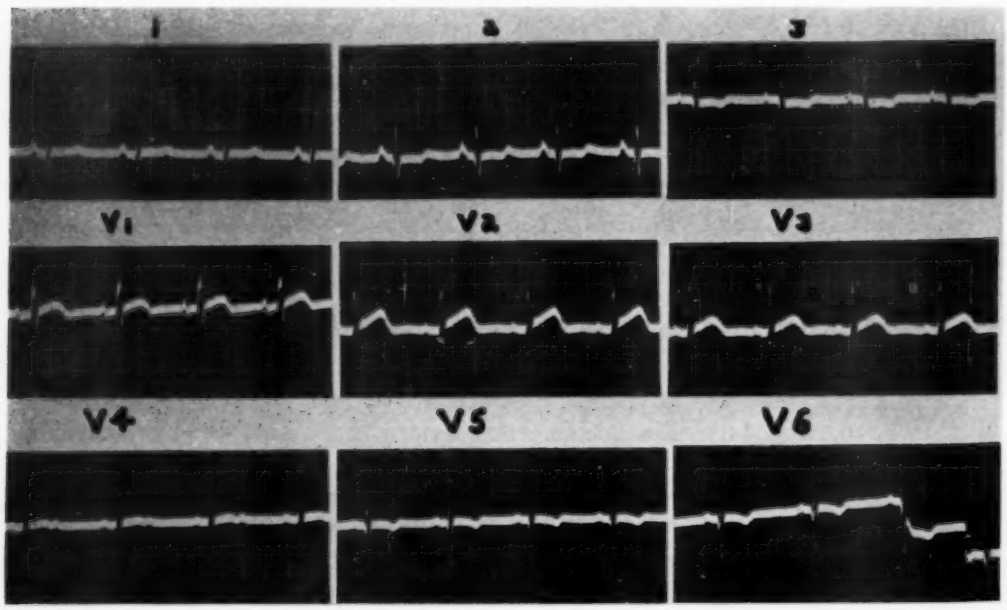

Fig. 11 (R. M.).—Regular sinus rhythm. Slurring upstroke QRS_3, ∓ T_3. Clockwise rotation Inverted T in V_4-V_6. In aV_R, small R, upright T. In aV_L, inverted T. In aV_F, sagging S-T, ∓ T.

There were single instances of pericardial effusion, parasystolic ventricular rhythm, and sinus arrhythmia. A positive family history was elicited in two of the cases; the average age of onset was 4 years. Only one patient showed evidence of congestive failure. The electrocardiograms were abnormal in the five cases in which they were taken. We conclude that involvement of the coronary arteries of the left ventricle may play a decisive role in the production of myocardial fibrosis.

Diastolic murmurs (either proto-, mid-diastolic, or presystolic) were described previously in cases reported by Pitt,[2] Debbasch and associates,[5] Van Bogaert and Van Bogaert,[7] and Hejtmancik and associates.[14] In the latter two reports, the presystolic murmur was heard best after exercise, signifying that tachycardia and velocity of blood flow plays a role in its cause. Hypertrophy and dilitation of the left ventricle with its resultant effect on the mitral valve may be the mechanism of production of the presystolic murmur.

In our report of Case N.S., there were a protodiastolic, presystolic, and early systolic murmurs associated with paroxysmal episodes of auricular tachycardia, and rheumatic carditis with mitral stenosis was suspected. But, on the basis of the above reports with the negative findings on autopsy, we should favor the belief that this is not a rheumatic cardiac involvement and thus we should not expect to find valvular lesions, if and when, the patient should come to autopsy.

We believe that the clinical picture and electrocardiographic studies on our comparatively large series of eleven cases bear out the results found by the aforementioned authors. Symptoms, congestive failure, and paroxysmal bouts of tachycardia, referable to the cardiovascular system, are present in the minority of cases as compared to those who lack symptoms. Murmurs present over the mitral, aortic, and pulmonic areas are not accountable by organic valvular damage as noted in the numerous autopsies. Atheromatous involvement of the coronary arteries may or may not be present; diffuse interstitial myocardial fibrosis has been seen in cases without involvement of the coronary arteries. Electrocardiographic changes (as previously described) are almost invariably present in a typical pattern. The presence of a diastolic murmur which is audible on exercise has been heard on several occasions. Death of the patient is generally caused by congestive failure or an intercurrent infection such as pneumonia. The findings of the autopsy of the present case are in complete accord with those previously reported.

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THE KREBS CYCLE IN HUMAN CARDIAC MUSCLE

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AFTER demonstrating the feasibility of obtaining biopsies of the human myocardium,[2,3] tissue provided by removing the auricular appendage has been used to study intermediary metabolism of this muscle. Since the tricarboxylic acid cycle[5-7,10-12,15,23,24] may be a common pathway in carbohydrate, fat, and protein metabolism,[10,16] it is a logical point to begin a series of studies designed to investigate the conversion of metabolites into energy directly rather than through animal experimentation. The results of experiments to find whether or not the Krebs cycle is operative in the aerobic metabolism of human myocardium are recorded in this communication.

METHODS*

Muscle from the auricular appendage was obtained at the time of thoracotomy in twelve patients. The appendage was removed from the beating heart and immediately placed in a Petri dish resting on ice. Slices 0.5 mm. thick were cut rapidly with a Stadie-Riggs slicer after connective tissue and fat had been trimmed away from the sample. Respiration of the slices was determined by the direct method of Warburg, using oxygen as the gas and Krebs-Henseleit physiological saline (with 2.4 meq./L. Ca) as the medium. Substrate was added from the side arm at the end of the equilibration period. The average weight of wet tissue used in each vessel was 76.0 milligrams.

The effect of the sodium salt of pyruvic, β-hydroxybutyric, acetic, citric, α-ketoglutaric, succinic, fumaric, malic, and fumaric plus pyruvic acids on oxygen consumption of the slices was studied in separate determinations. After this was done, possible inhibitory action of malonate and arsenite were tested. Slices were incubated with sodium malonate and the sodium salts of pyruvic, citric, malic, and pyruvic plus fumaric acids added in respective vessels. Concentrations of substrates may be found in Tables I and II. In another series of vessels, oxygen consumption of the human cardiac slices was measured in the presence of 0.001M sodium arsenite plus 0.07M sodium citrate.

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Finally citric, α-ketoglutaric, and succinic acid determinations were made with and without appropriate inhibitor added to the muscle slices. Citric acid values were obtained for control vessels by the method described by Perlman, Lardy, and Johnson,[17] and these values were compared to the citric acid content when the muscle was incubated in an atmosphere of nitrogen. The nitrogen was passed over heated copper turnings before introduction into the Warburg flasks. The substrate used in both aerobic and anaerobic studies was 0.02M sodium oxalacetate. Other slices were used to find the amount of α-ketoglutaric acid present when the muscle was respiring in a substrate of 0.07M sodium citrate with and without 0.001M sodium arsenite added as an inhibitor. The amount of succinic acid after incubation of the tissue with and without 0.025M sodium malonate was also determined. The substrate used was 0.02M sodium pyruvate plus 0.0025M sodium fumarate. Manometric methods outlined by Cohen[21] were followed in determining both succinic and α-ketoglutaric acids.

TABLE I. EFFECT OF PYRUVATE, β-HYDROXYBUTYRATE, AND INTERMEDIATES IN THE KREBS CYCLE ON RESPIRATION OF HUMAN CARDIAC MUSCLE

NO. OF DETERMINATIONS	SUBSTRATE	MINUTES								
		30	60	90	120	150	180	210	240	270
11	Control	1.7*	3.1	4.2	5.4	6.4	7.2	8.3	9.3	10.4
3	0.02M Na pyruvate	2.7	5.0	7.0	9.1	10.6	12.2	14.0	15.7	17.4
2	0.02M Na β-hydroxybutyrate	2.2	4.2	6.0	8.4	9.7	11.4	13.3	15.8	16.9
1	0.02M Na acetate	2.0	3.6	5.3	7.0	8.1	9.5	11.4	12.5	14.1
1	0.02M Na citrate	2.0	4.8	7.2	9.5	11.1	12.2	12.9	14.5	15.5
1	0.02M Na α-ketoglutarate	2.3	4.8	7.7	10.8	13.2	15.1	19.7	22.0	25.1
1	0.01M Na succinate	3.2	7.3	11.6	16.6	20.8	25.7	29.4	33.8	37.0
1	0.03M Na fumarate	1.6	2.8	4.4	6.8	7.5	7.7	10.4	11.6	13.6
2	0.02M Na malate	1.9	3.9	6.1	8.6	10.2	12.6	14.2	16.6	18.5
2	0.03M Na fumarate + 0.02M Na pyruvate	2.0	4.0	6.2	9.1	11.1	12.5	15.2	17.4	20.4

*Mean c.mm. O_2 consumed per milligram dry weight of tissue.

RESULTS

Addition of the sodium salt of pyruvic, β-hydroxybutyric, acetic, citric, α-ketoglutaric, succinic, fumaric, malic, and fumaric plus pyruvic acids to the saline medium resulted in increased oxygen consumption by slices of human cardiac muscle in each case. This is shown in Table I where the respiration is recorded as the mean c.mm. of oxygen consumed per milligram dry weight of the tissue. The cumulative value for oxygen uptake varies from 13.6 c.mm. in 4.5 hours in the presence of sodium fumarate to 37.0 c.mm. during the same period of time when sodium succinate was added. The average amount of oxygen consumed by the slices was greater in the presence of each of these substrates than in the absence of exogenous substrate in eleven control determinations, which increased from 1.7 ± 0.6 c.mm. of oxygen consumed per milligram of dry tissue in 30 minutes to 10.4 ± 3.6 c.mm. in 4.5 hours. When the data for each heart were

considered separately, it was found that in all except one instance the oxygen uptake was greater when substrate was added than when muscle from the same heart was incubated in saline alone. In this instance 0.65 c.mm. more oxygen per milligram of dry tissue was consumed by the slices in saline than in saline plus 0.03M sodium fumarate at the end of 4.5 hours. However, fumarate removed malonate inhibition of pyruvate oxidation when present in sufficient quantity (Table II).

TABLE II. EFFECT OF MALONATE ON RESPIRATION OF HUMAN CARDIAC MUSCLE

NO. OF DETERMINATIONS	SUBSTRATE	MINUTES								
		30	60	90	120	150	180	210	240	270
11	Control	1.7*	3.1	4.2	5.4	6.4	7.2	8.3	9.3	10.4
2	0.1M Na malonate	2.3	3.6	4.0	4.4	4.8	4.9	5.0	6.0	6.0
1	0.1M Na malonate + 0.02M Na pyruvate	1.0	1.7	2.4	3.3	4.2	5.0	5.9	6.8	
1	0.1M Na malonate + 0.02M Na citrate	2.5	4.8	5.3	6.7	6.8	6.8	6.8		
2	0.1M Na malonate + 0.02M Na malate	1.5	3.0	3.6	4.1	4.3	4.3	4.5	4.6	
4	0.025M Na malonate + 0.02M Na pyruvate + 0.0025M Na fumarate	2.6	4.0	6.1	7.6	8.2	9.3	9.6		
1	0.025M Na malonate + 0.02M Na pyruvate + 0.025M Na fumarate	3.3	5.4	7.4	10.3	12.4	15.3	18.9		

*Mean c.mm. O_2 consumed per milligram dry weight of tissue.

When malonate was present, respiration was inhibited. This may be verified by comparing the values in Table II for oxygen consumption in the presence of malonate with sodium pyruvate, sodium citrate, and sodium malate to corresponding values for oxygen uptake in Table I without malonate. For example, the number of c.mm. of O_2 consumed per milligram dry weight of the tissue was 15.7 in four hours in the presence of pyruvate and only 6.8 in the same length of time when sodium malonate was added to the sodium pyruvate. That addition of sufficient substrate may overcome this inhibition is illustrated by the increase in oxygen consumption of the slices to control levels when fumarate was present in 0.025M concentration (Tables I and II). This may be contrasted to the smaller oxygen uptake when fumarate in 0.0025M concentration was present with the inhibitor and sodium pyruvate. Similar results were reported by Krebs and Eggleston[11] who found that fumarate removes malonate inhibition of the oxidation of pyruvate by minced pigeon breast muscle.

Little evidence that 0.001M sodium arsenite inhibited oxygen consumption of the slices in the presence of 0.07M sodium citrate (Table III) was obtained. At the end of 3.5 hours an average of 14.4 ± 3.3 c.mm. of oxygen per milligram dry

weight of the muscle had been consumed by slices immersed in saline with arsenite and citrate compared to an average of 8.3 ± 3.1 c.mm. of oxygen consumed by muscle in saline alone.

TABLE III. EFFECT OF ARSENITE ON RESPIRATION OF HUMAN CARDIAC MUSCLE

NO. OF DETERMINATIONS	SUBSTRATE	MINUTES								
		30	60	90	120	150	180	210	240	270
11	Control	1.7*	3.1	4.2	5 4	6.4	7.2	8.3	9.3	10.4
5	0.001M Na arsenite + 0.07M Na citrate	2.4	4.2	6.5	8.7	10.4	12.6	14.4		

*Mean c.mm. O_2 consumed per milligram dry weight of tissue.

Table IV contains the difference between the amounts of citric, α-ketoglutaric, and succinic acids found in slices of human heart muscle with and without inhibition by anaerobiosis, arsenite, and malonate, respectively. Each acid was found in greater concentration when inhibitor was present. An average increase of 0.79 mg. of citric acid per 100 milligrams of tissue per hour was found when slices were incubated with oxalacetate in an atmosphere of nitrogen. The average amount of α-ketoglutaric acid accumulated (3.55 mg. per 100 milligrams of tissue per hour) after addition of arsenite and the average amount of succinic acid accumulated (2.25 mg. per 100 milligrams of tissue per hour) after addition of malonate also are convincing evidence for the inhibitory action of arsenite and malonate, respectively.

TABLE IV. INHIBITION OF KREBS CYCLE AND ACCUMULATION OF INTERMEDIATES

Inhibitor	N_2 Anaerobiosis	0.001M Na arsenite	0.025M Na malonate
Substrate	0.02M Na oxalacetate	0.07M Na citrate	0.02M Na pyruvate 0.0025M Na fumarate
Intermediate Accumulated	Citric acid	α-Ketoglutaric acid	Succinic acid
	0.52*	3.19	0.48
	0.32	3.12	1.28
	0.62	5.39	2.87
	0.53	2.52	3.85
	1.27		2.79
	1.49		
Mean	0.79	3.55	2.25

*Mg. per 100 milligrams of tissue per hour.

DISCUSSION

The Krebs cycle in modified form is depicted in Fig. 1. It is a common final pathway in the aerobic conversion of many metabolites to carbon dioxide and water and has been found to operate in a number of tissues, including cardiac

muscle,[19] since the original observations of Krebs and Johnson[10] who used minced muscle from pigeon breast. Following glycolysis and the formation of pyruvate, carbohydrate may be metabolized by this route. Oxidative decarboxylation of pyruvic acid probably yields an active acetyl residue which is transported by coenzyme A and condenses with oxalacetic acid to yield a tricarboxylic acid.[15] With each complete turn, one molecule of pyruvic acid is completely oxidized, but the intermediates in the cycle are reconstituted and are then available for the oxidation of another molecule of pyruvate. One important outcome of this process is generation of the energy-rich phosphate bond of adenosine triphosphate. The points in the chain of reaction at which inhibition by nitrogen, arsenite, and malonate occur are indicated in the figure. The position of the tricarboxylic acids in Fig. 1 is rather arbitrary since the relation of citric acid to the cycle is still controversial.[15,20]

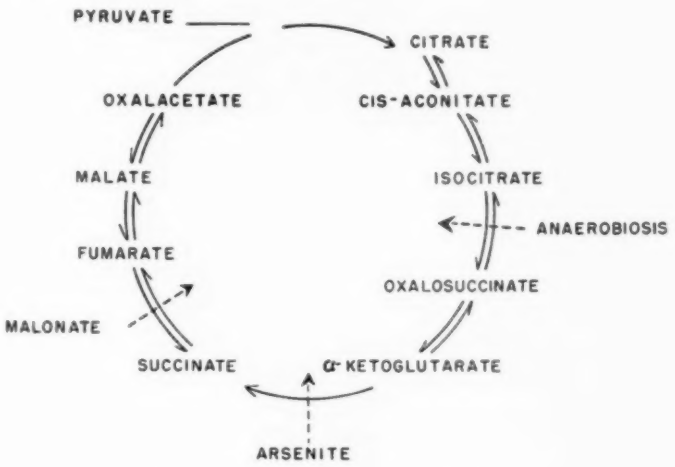

Fig. 1.—Krebs tricarboxylic acid cycle.

The C_2 compound formed as a result of the decarboxylation of pyruvate in the initial phase of the Krebs cycle may also be formed by the oxidation of fatty acids,[7,13,14] β-keto acids,[1,22] and acetate.[4,9,16] In addition to this role in the metabolism of fats, there are several indications, such as the formation of intermediates in the cycle by deamination of certain amino acids, that the Krebs cycle may also be a pathway in protein breakdown.

The question of whether the tricarboxylic cycle operates in human cardiac muscle may now be considered. The evidence accumulated in these experiments is of two types: (1) the effect of intermediates of the Krebs cycle on oxygen consumption of cardiac muscle slices has been tested, and (2) the effect of inhibitors on oxygen uptake of the slices and on accumulation of intermediates in the cycle has been studied. Although not all known intermediates of the cycle have been used, a representative group tested and recorded in Table I causes increased oxygen consumption of the muscle. A relative excess at any of these steps distributed around the connected chain of reactions results in increased

aerobic respiration, probably continuing until only catalytic quantities of each substance remains. The utilization of the intermediates by the muscle suggests that such a cycle is one of the terminal mechanisms of respiration in the human heart, particularly since the Krebs cycle is not ordinarily reversible. The specificity of the effect of each intermediate on respiration of the slices is indicated by the finding in other experiments that aconitate does not increase oxygen consumption of the muscle (*cis*-aconitate is known to be intermediate in the conversion of citrate to isocitrate).

Anaerobiosis is known to suppress the dehydration of isocitric acid, and the increased amount of citric acid found in an atmosphere of nitrogen probably was the result of that effect, citric acid itself being formed secondarily by the action of aconitase on accumulated *cis*-aconitate. No detailed studies on the exact relation of citric acid to the cycle were made.

Although respiration of the slices is not decreased by arsenite (Table III), there is an accumulation of α-ketoglutaric acid when arsenite is added to a preparation of muscle in saline containing sodium citrate (Table IV). This may be explained by inhibition of oxidative decarboxylation due to the arsenite with failure to form succinate.

The accumulation of succinic acid and decreased oxygen consumption of the muscle in the presence of malonate (Tables II and IV) may be explained by the inhibitory effect of malonate on succinic dehydrogenase blocking the cycle at succinic acid so that formation of fumaric acid is inhibited and succinic acid is accumulated.

The behavior of the muscle on addition of the intermediates in the cycle and after inhibition by anaerobiosis, arsenite, and malonate leads reasonably to the conclusion that the Krebs cycle operates in human cardiac muscle. In addition to explaining the aerobic oxidation of carbohydrate from the point at which pyruvate is formed, it may also be a pathway in the oxidation of fat if the effect of sodium acetate and sodium β-hydroxybutyrate may be used as an indication, and, at least theoretically a route in the utilization of protein. This mechanism should serve as a suitable point of departure in studying the intermediary metabolism of this vital tissue.

CONCLUSIONS

1. Addition of pyruvate, β-hydroxybutyrate, acetate, citrate, α-ketoglutarate, succinate, malate, and pyruvate plus fumarate to slices of human cardiac muscle resulted in increased oxygen consumption of the slices.

2. Citric acid content was greater when slices of muscle were incubated anaerobically than when they were incubated aerobically with oxalacetate.

3. The addition of sodium arsenite to slices of human muscle in the presence of citrate resulted in the accumulation of α-ketoglutaric acid. The oxygen consumption of the tissue under these circumstances was not reduced.

4. When malonate was added to human cardiac tissue incubated with pyruvate, citrate, malate, and pyruvate plus 0.0025M fumarate, increased respiration previously noted was inhibited.

5. Addition of malonate to samples of muscle in a medium containing pyruvate and fumarate caused an increase in the amount of succinic acid present.

6. The results of this study indicate that the Krebs cycle is operative in the intermediary metabolism of human cardiac muscle.

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CRITICAL RATES IN VENTRICULAR CONDUCTION. IV.

Duration of Unstable Bundle Branch Block

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IN 1941 one of us described a condition of unstable ventricular conduction noted in some patients with myocardial disease and closely related to a critical cardiac rate.[1] At this critical rate there apparently existed in a bundle branch a delicate state of equilibrium between normal conduction and nonconduction or block, which was sensitive to slight variations in cardiac rate. Often as little as an increase or decrease of one beat per minute changed conduction to block, or block to conduction. Several changes back and forth might take place within the period of a minute or two. This condition has been observed many times since. The following case exhibits the longest duration on record of unstable bundle branch block. Because of the extraordinarily long period, ten and one-half years, during which fluctuations back and forth between normal conduction and bundle branch block existed, certain explanations of the mechanism involved are supported,[1] and it is suggested these may also be applicable to other forms of nonpermanent bundle branch block.

CASE REPORT

P.M., a 55-year-old white man, married, and a business executive, was first examined about ten years ago, Dec. 27, 1941. His sole complaint at that time was slight dull precordial discomfort for one month, unrelated to food or physical effort. He also wished to check a recent diagnosis of hypertension. His past history revealed no significant medical or surgical illness except a low-grade chronic prostatitis, and injuries to the right groin (1942), left shoulder (1944), and pelvis (1947), sustained horseback riding. He smoked about six cigars daily. On examination in 1941 he appeared well, and there was no dyspnea or cyanosis. The heart revealed no enlargement. The heart sounds at the apex were of normal intensity and duration. The aortic second sound was louder than the pulmonary second sound, but not accentuated. A short Grade I blowing systolic murmur was heard over the aortic valve area. It was poorly transmitted. The blood pressure was 160/102 mm. Hg. The urine contained occasional pus clumps. The electrocardiogram showed a right bundle branch block with a deep QS in Lead III.

During the ten and one-half years up to the present, he was examined regularly at the office several times a year for the purpose of checking the blood pressure, electrocardiogram, and general medical status. He worked regularly and took no time off for illness, except in 1947 because of the injury to the pelvis.

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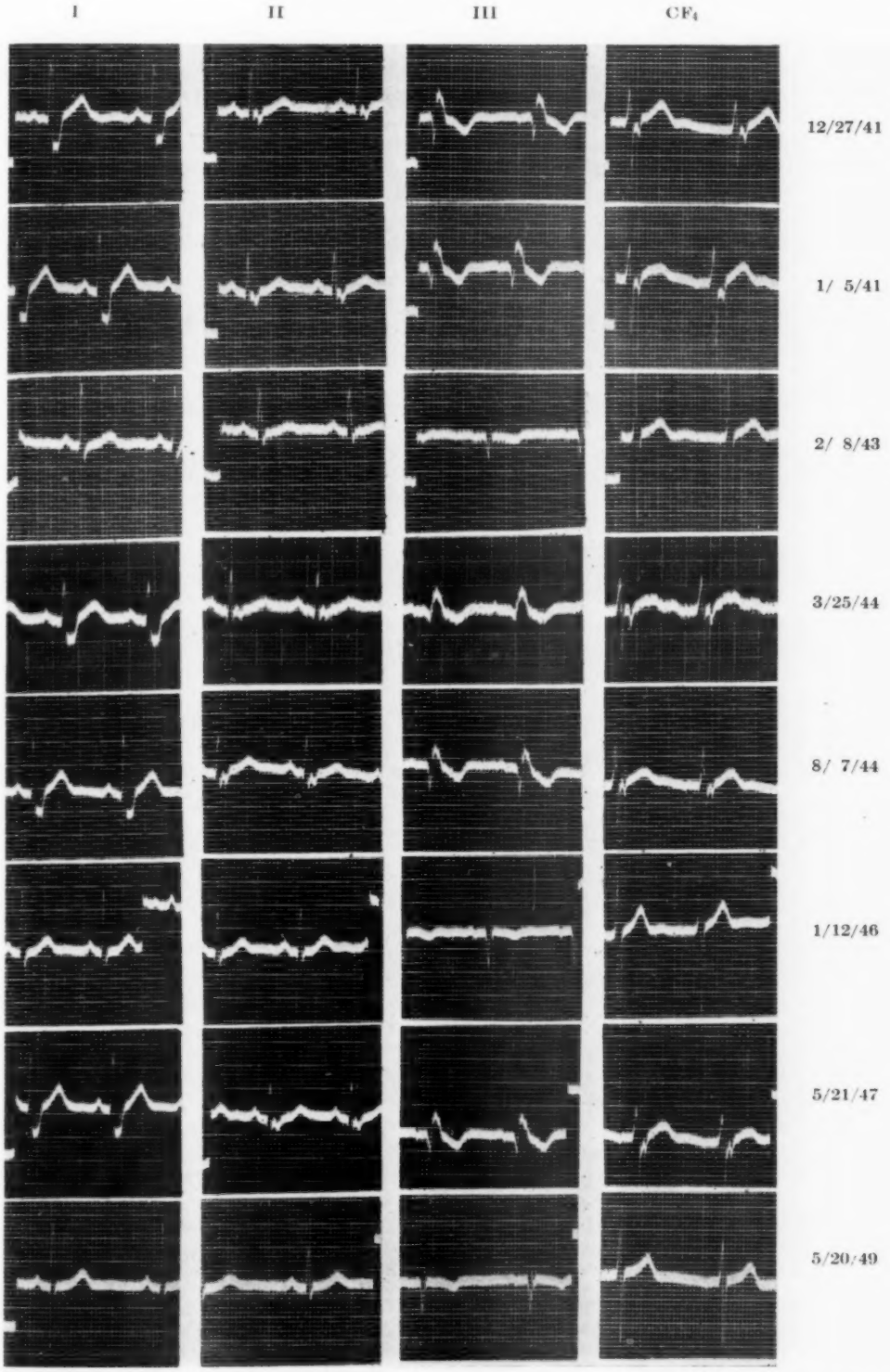

Fig. 1.—Electrocardiograms revealing bundle branch block and normal ventricular conduction at different dates. For description see text.

On physical examination (June, 1952) he appeared as a healthy looking mesomorphic type man, 55 years of age, with ruddy complexion. There was no arcus senilis. The pupils reacted to light and accommodation; the fundi revealed a slight increase in tortuosity of the small arteries with a slight increase in the central white line. There was no thyroid enlargement; the neck veins were not unduly filled. Heart sounds and murmurs were as described above; the blood pressure in the arms was systolic 158 to 180, diastolic 92 to 110 mm. Hg. The lungs were clear. Respirations were normal. The liver and spleen were not palpable. A small right inguinal hernia was palpable. There was no edema of the extremities; the dorsalis pedis pulsations were normal. The prostate was slightly large and smooth but not hard. Reflexes were physiologic.

Laboratory Data.—Routine examination of the urine was negative. The red and white blood cell counts were normal. Blood glucose was 115 mg., blood nonprotein nitrogen 41 mg., cholesterol 204 mg., and uric acid was 3.4 mg. per 100 c.c. of blood. The blood Wassermann was negative.

Teleroentgenogram of the chest revealed the heart in the semihorizontal position. There was no evidence of enlargement of the cardiac chambers. The entire thoracic aorta seen in the anteroposterior position appeared slightly dilated. The lungs were clear. The electrocardiogram showed a W-shaped QRS in aV_F, the Q being 0.04 second, and equal or larger than the varying small R; but QR was only 3.4 mm. In a semihorizontal heart this, with the prominent Q_3, was not diagnostic electrocardiographically of posterior wall infarction. However, it was suggestive of this, and so fitted into the clinical diagnosis. The diagnosis was essential hypertension, arteriosclerotic heart disease with an old posterior wall infarction, but good cardiac function.

Over the ten and one-half year period to the present, sixteen electrocardiograms were taken; one or more each year except in 1945 and 1950. Until 1949 each electrocardiogram consisted of four leads—the three standard limb leads and one precordial lead, CF_4. Thereafter, twelve leads were taken each time: the three standard limb leads, leads aV_R, aV_L, aV_F, and V_1 through V_6. Tracings were taken with the patient in the sitting and recumbent position. The Cambridge string galvanometer or the Sanborn Visocardiette were used. Sensitivity was 1 cm. for 1 millivolt. A hand lens helped obtain measurements to within 0.005 second.

The first electrocardiogram was taken on Dec. 27, 1941 (Fig. 1). It showed the presence of bundle branch block of the wide S_1 type of Wilson[2]—type III right bundle branch block of Bayley.[3] S_1 was 0.09 second, R_1 was 0.05 second, and R was larger than S in Lead I. Twenty-eight cycles were recorded. The rate was 63 to 65 per minute. All QRS complexes were wide (0.14 second).

The second tracing was taken on Jan. 5, 1942, nine days after the first, and it was similar. All QRS waves were wide. The cardiac rate, however, was faster—75 to 80 per minute.

The third tracing, taken Aug. 1, 1942, showed a change. Normal QRS complexes, 0.08 second, now were present in the three standard limb leads, with the exception of two consecutive wide QRS waves in Lead I (Fig. 2). These two were terminal to cycles (R-R intervals) of 0.84 second, which were faster than the rest of the beats in the three standard leads where the R-R intervals were 0.85 to 0.90 second. In the precordial lead, CF_4, all the ventricular complexes were of the bundle branch block variety. The R-R intervals here were 0.79 to 0.84 second for the eight cycles recorded. In this entire four-lead tracing there were twenty QRS complexes at a rate of 65 to 71 per minute and all of normal width. Nine QRS complexes were in faster cycles—71 to 76 per minute and all these were wide. Except for two complexes in Lead I, this tracing fortuitously simulated localized bundle branch block, an occurrence previously described.[1]

In the fourth electrocardiogram, Feb. 18, 1943, the cardiac rate was 67 to 71, and the ventricular complexes in all four leads were of normal duration.

In the fifth and the sixth tracings, March 25, 1944, and Aug. 7, 1944, all QRS complexes in all the leads were wide. The cardiac rates were 88 to 92.5 per minute in the former and 71 to 77 per minute in the latter.

The seventh tracing was taken on Jan. 12, 1946, about four years after the first. The rate was 69 to 71 and all QRS complexes were of normal duration.

In the eighth tracing, May 21, 1947, the rate was 75 to 78 and all QRS complexes were wide.

In the ninth electrocardiogram, Oct. 15, 1948, the cardiac rate was slow. It was 61 to 62 for thirty of the thirty-two cycles recorded and in these thirty the QRS was normal in duration. Two cycles were only very slightly faster, 62.5 and 63 per minute, and here the two QRS waves were wide. At this time the critical rate was about 62.5 per minute (Fig. 3).

In the tenth tracing, May 20, 1949, the cardiac rate was slow, 56 to 59 per minute, and all QRS waves were normal in width. Some exercise did not raise the rate over 62.5 when the electrocardiogram was recorded, and the QRS remained normal.

The eleventh, twelfth, thirteenth, and fourteenth electrocardiograms were taken between January and December, 1951, and the fifteenth on Jan. 21, 1952 (Fig. 4). All QRS waves in all five tracings were wide with the same aberration as ten years earlier. The cardiac rates ranged from 62.5 to 79 per minute except in one tracing on March 14, 1951, when the rate was 58 to 61. Rest in bed for one hour, carotid sinus and ocular pressure, and Prostigmin were used in an attempt to slow the cardiac rate further and induce normal ventricular conduction. Little slowing was effected, and the bundle branch block persisted.

Fig. 2.—Electrocardiogram taken Aug. 1, 1942. Varying ventricular conduction with a critical cardiac rate. See text for description.

Another attempt to induce slowing of the cardiac rate and normal QRS waves was made on June 3, 1952. The patient was put to bed and allowed to fall asleep. He slept about one hour and then was gently awakened when the electrocardiographic electrodes were applied. The routine twelve-lead electrocardiogram was taken (Fig. 5). One hundred thirty-five cycles were recorded with a cardiac rate from 61 to 69 per minute. All QRS waves now were normal in duration, (0.08 second). Exercise was then performed by the patient. From the standing position, body bending was done about fifteen times. The electrocardiogram was promptly recorded with the patient in

the recumbent position. The first seven QRS complexes were of the bundle branch block type (Fig. 6). In the six cycles so formed, the R-R intervals were 0.70, 0.70, 0.74, 0.75, 0.75, and 0.77 seconds (86 to 78 per minute). The seventh cycle R-R was 0.80 second (75 per minute) and terminated in a normal QRS wave. The succeeding cycle lengths (R-R) were 0.80, 0.78, 0.81, and 0.81 seconds with the five QRS waves appearing normal. Thus all cycles 0.77 second or faster showed bundle branch block and those 0.78 second or slower had normal QRS complexes, in-

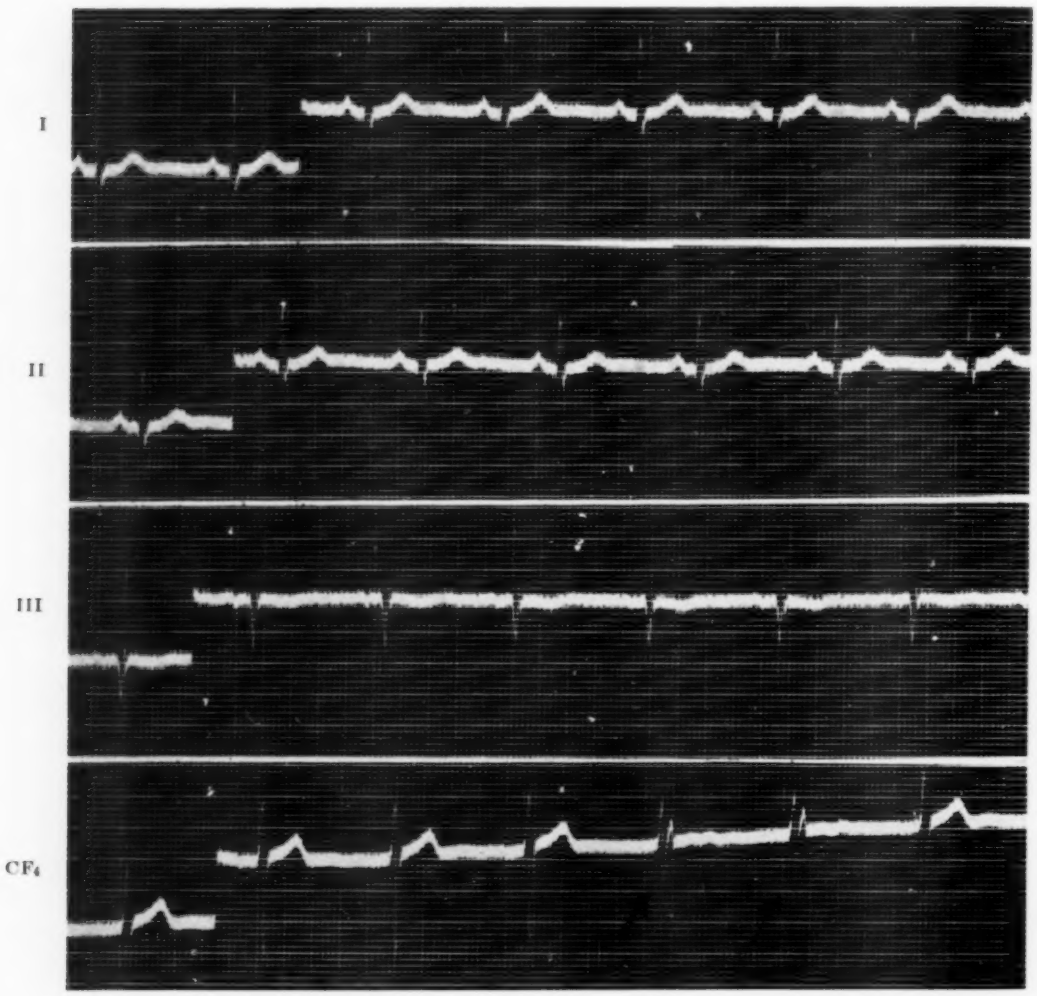

Fig. 3.—Electrocardiogram taken Oct. 15, 1948. Changes in ventricular conduction at a critical cardiac rate in Lead CF_4. See text.

dicating the presence of a critical rate between 77 and 78 per minute (R-R, 0.78 to 0.77 second). Lead II was then recorded. All thirteen QRS complexes here were normal. The twelve cycles of this lead ranged in rate from 72 to 77 per minute (R-R, 0.84 to 0.78 second). Lead III had nine QRS waves, all 0.08 second. The eight cycles ranged from 71 to 73 per minute (R-R, 0.84 to 0.82 second).

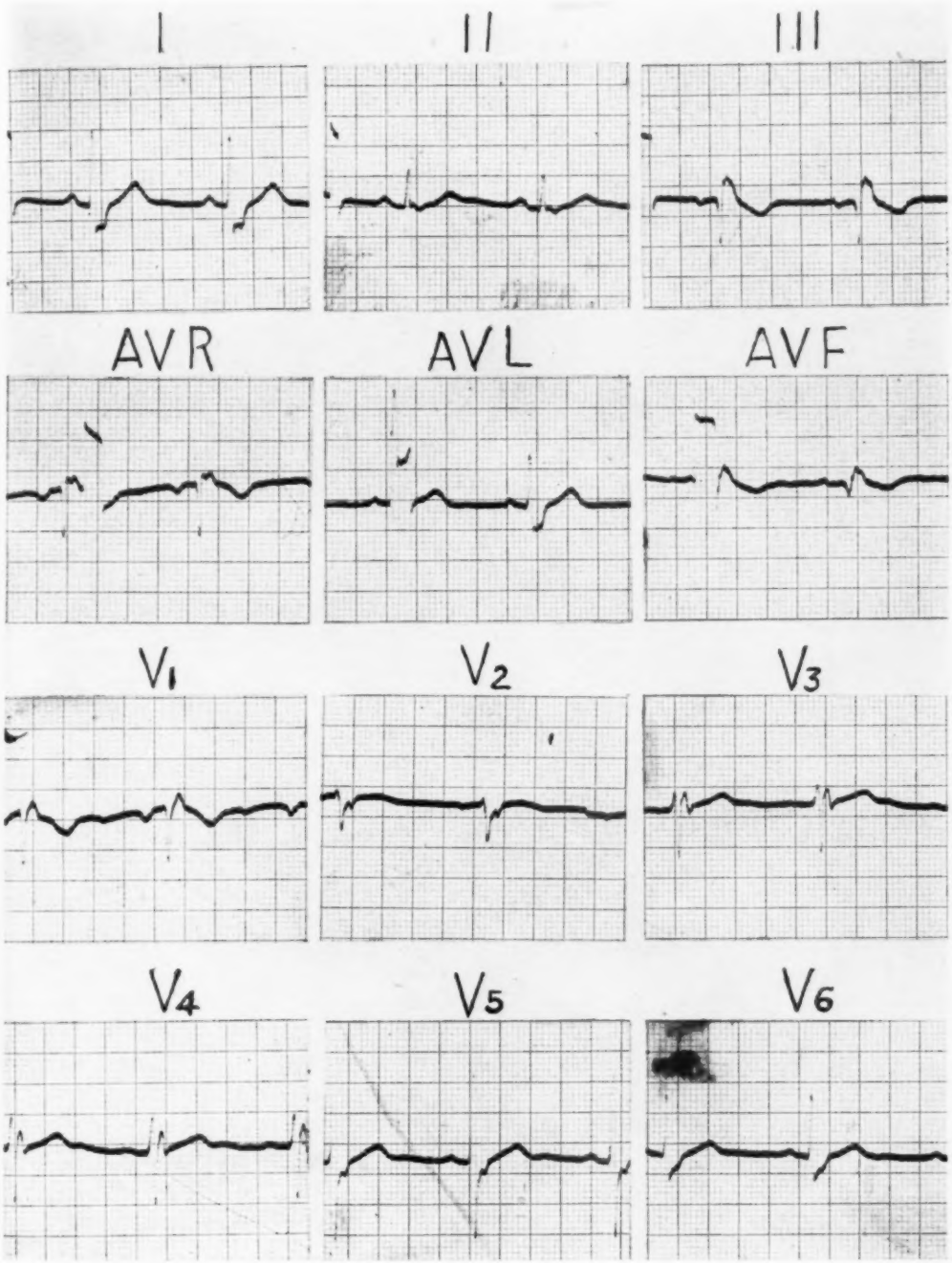

Fig. 4.—Electrocardiogram taken Jan. 21, 1952. Bundle branch block complexes are present in all twelve leads.

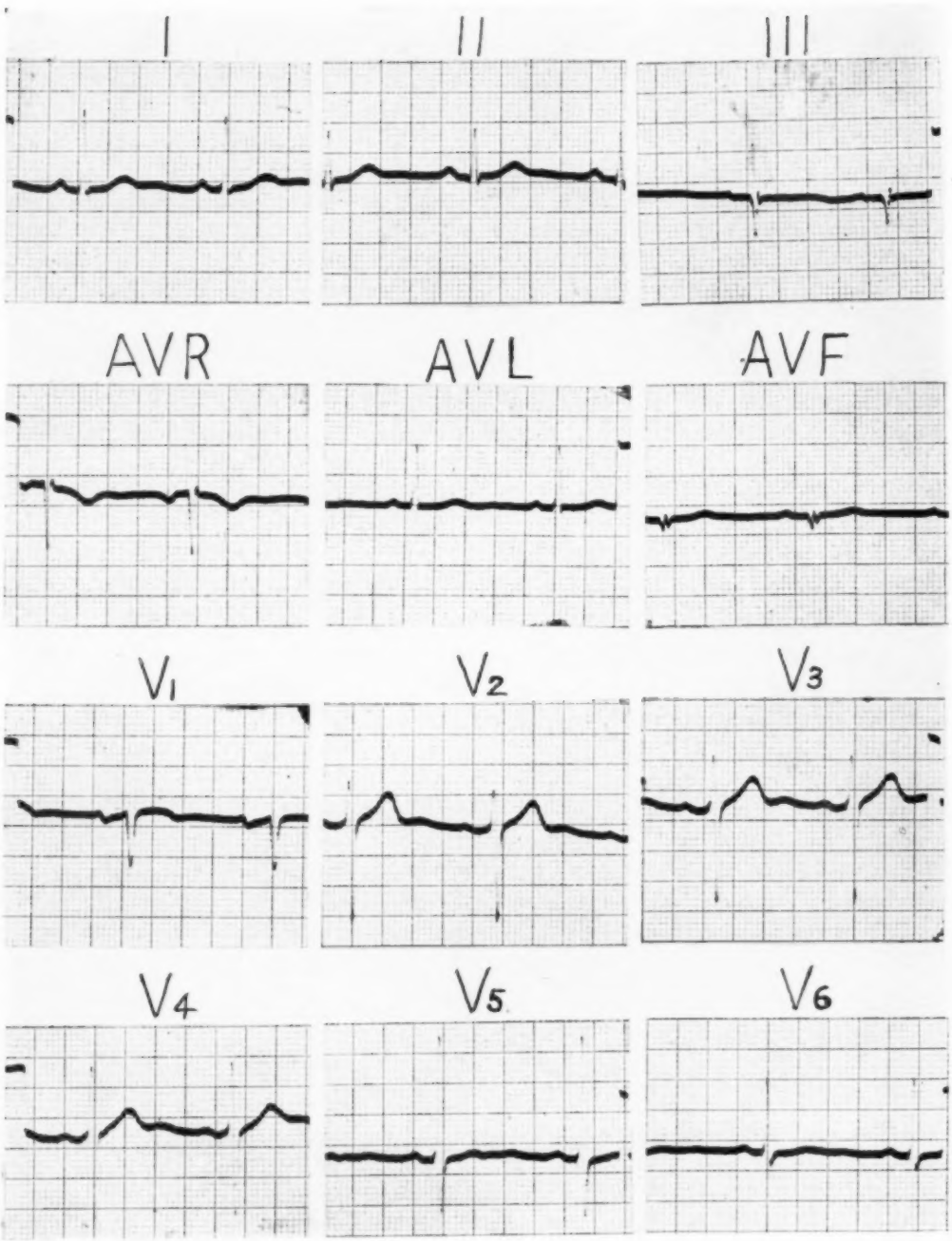

Fig. 5.—Electrocardiogram, June 3, 1952, taken after resting. All the complexes in the twelve leads reveal normal ventricular conduction.

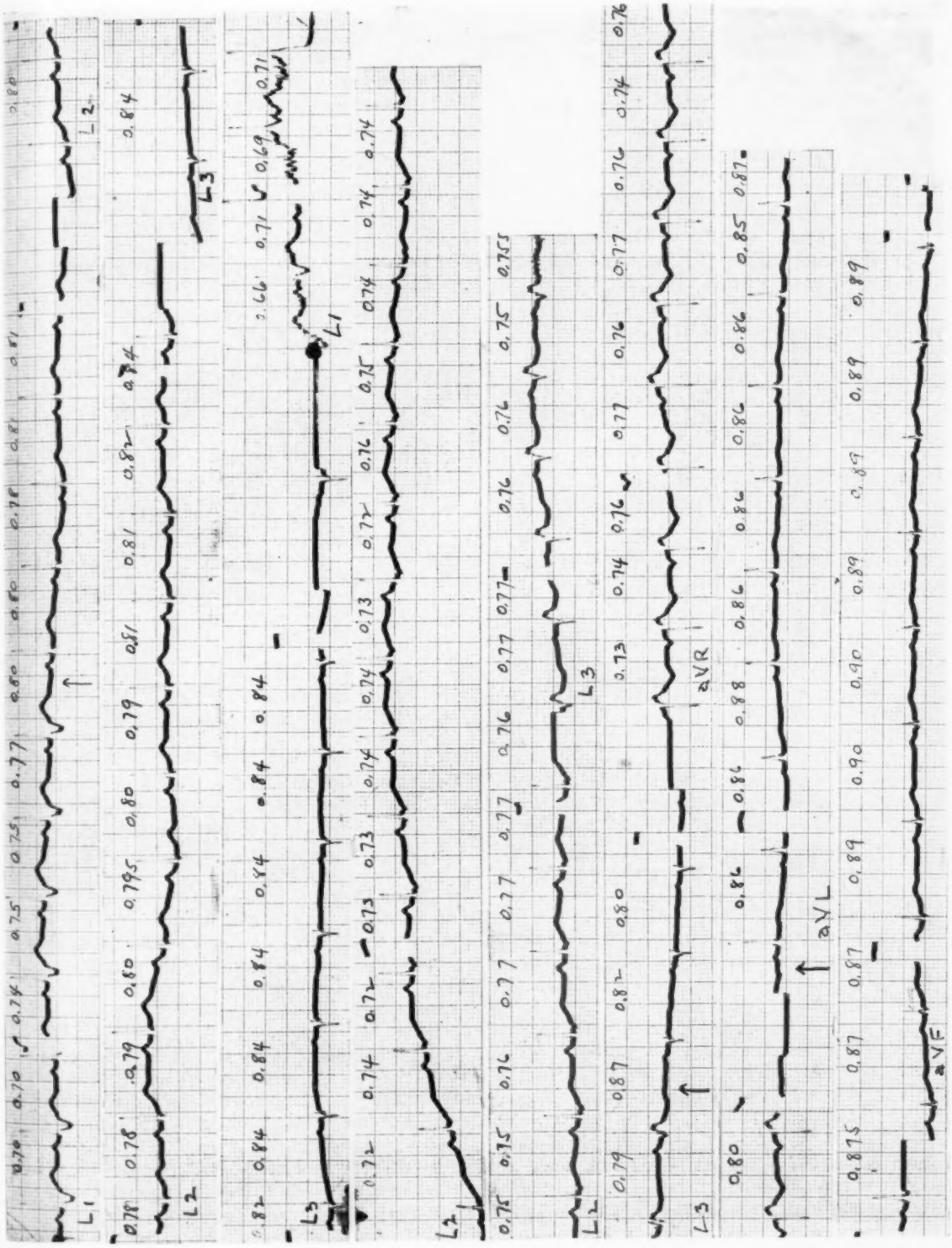

Fig. 6.—Electrocardiogram, June 3, 1952, taken after exercise. See text.

Another bout of exercise similar to the first was performed, and the electrocardiogram was again recorded with the patient in the recumbent position. In Lead I all five QRS complexes were wide. The rate was 84.5 to 91 per minute (R-R, 0.71 to 0.66 second). In Lead II there were twenty-two cycles, all with wide QRS waves and a rate of 78 to 86 per minute (R-R, 0.77 to 0.70 second). In Lead III the rate continued to slow with gradually increasing cycle lengths, from R-R of 0.76 to 0.79 second. In the seven cycles, all the eight QRS complexes were wide. The eighth cycle (R-R) was 0.87 second and the next and final two cycles in this lead were 0.82 to 0.80 second, these last three QRS complexes were each of normal duration. The critical rate here was between 75 and 76 per minute (R-R, 0.80 to 0.79 second). In Lead aV_R, taken next, the rate became slightly faster, the ten cycles ranged between 78 and 82 per minute—faster than the critical rate; again all the QRS complexes were wide. Leads aV_L and aV_F were taken next. Nineteen cycles were recorded. The rate during this period was slower, 67 to 71 per minute, and here all QRS waves were normal in width.

TABLE I.

DATE	R-R INTERVAL	RATE PER MINUTE	VENTRICULAR CONDUCTION
12/27/41	0.955 to 0.92	63 to 65	Block
1/5/42	0.80 to 0.75	75 to 80	Block
8/1/42	0.90 to 0.85	65 to 71	Normal
	0.84 to 0.79	71 to 76	Block
2/15/43	0.90 to 0.845	67 to 71	Normal
3/25/44	0.68 to 0.65	88 to 92.5	Block
8/7/44	0.85 to 0.78	71 to 77	Block
1/12/46	0.87 to 0.84	69 to 71	Normal
5/21/47	0.80 to 0.77	75 to 78	Block
10/15/48	0.99 to 0.97	61 to 62	Normal
	0.96 to 0.95	62.5 to 63	Block
5/20/49	1.07 to 1.01	56 to 59	Normal
After exercise	0.96	62.5	
1/15/51	0.94 to 0.89	64 to 67	Block
3/14/51	1.04 to 0.98	58 to 61	Block
9/15/51	0.82 to 0.79	73 to 76	Block
12/22/51	0.82 to 0.76	73 to 79	Block
1/21/52	0.92 to 0.88	65 to 68	Block

Of the sixteen electrocardiograms taken during the ten and one-half years, eleven electrocardiograms were of the bundle branch block type. Three electrocardiograms showed only normal QRS complexes, and three electrocardiograms had both normal and wide QRS waves in each tracing. There was considerable variation in cardiac rate in all the electrocardiograms taken—a range from 56 to 92 per minute (Table I). On the five occasions when QRS waves of normal duration were observed, the cardiac rate was 56 to 71 per minute, no cycles were faster than 71 per minute. In seven other tracings the rate was 71 or faster in each, and in all of these records bundle branch block was present. In addition there were five tracings with bundle branch block and a cardiac rate slower than 71 per minute, but in none of these did normal QRS complexes appear at the same or faster rates than for bundle branch block complexes. In each of two tracings where both normal ventricular conduction and bundle branch block appeared together (Figs. 2 and 3), the normal QRS waves were present at the slower rates and bundle branch block at the faster rate with a critical rate for each transition of 71 per minute in tracing of Aug. 1, 1942, and 62.5 per minute in the tracing of Oct. 15, 1948. In the third tracing where both normal and wide QRS waves appeared, exercise had been performed. There were three changes from normal to bundle branch block as the cardiac rate got faster after exercise. The transitions from normal to bundle branch block with exercise were not recorded, but during the presence of bundle branch block the cardiac rate was always faster than 71 per minute. There were three changes from bundle branch block to normal QRS complexes as the cardiac rate slowed gradually after exercise. Each change was sudden, within the period of one cycle, without transitional complexes and occurred at critical rates of 77, 76 and 75 per minute.

DISCUSSION

The history and pathologic physiology of unstable block were discussed previously.[1,5] Functional changes of fatigue or recovery from fatigue were considered as probably responsible for the fluctuations between conduction and block. Rate changes acted as a trigger mechanism when other conditions in the bundle branch tissue were suitable. The critical rate might be almost any cardiac rate and has been found to be anywhere from about 40 to about 200 per minute.[1,5] It was different in different cases, but also varied in the same patient at different times. Its variations on the same day were very little, but on different days were greater.[6] Thus in one patient on different days the critical rate varied from 65 to 75 per minute.[1]

The incidence of unstable bundle branch block must be much greater than is apparent. In many ordinary cases of bundle branch block, a period of unstable conduction as described above might be revealed if the critical rate were sought and induced. This would apply to some cases of so-called permanent bundle branch block at some period in their clinical course, and more often to the many cases labeled transient, intermittent, recurrent, and functional bundle branch block. A number of these latter have been regarded as definitely unrelated to cardiac rate, and vagal action has been considered a cause of such changes in ventricular conduction.[7-14] The problem of the role of the vagus in ventricular conduction however is still unsettled.[15] In a recent review of nonpermanent bundle branch block, Hein and Sanazaro[16] concluded that the abolition of transient or intermittent bundle branch block following direct or reflex vagal stimulation must be considered entirely secondary to the concomitant cardiac slowing rather than to any vagal action on the conduction system. The effects of oxygen, digitalis, and rest, in resolving bundle branch block, are thought due merely to slowing of the heart rate beyond a critical point.[17] The exact local physiochemical mechanism of this dromotrophic effect however remains unknown. The pathologic anatomy of unstable bundle branch block has also been discussed previously.[1,5] Pathologic conditions responsible are probably the same as for permanent bundle branch block, and include any variety of disease or injury which can affect the bundle of His and its main branches. These form a large array of viral, bacterial, rheumatic, and congenital heart disease,[18-22] thyrotoxicosis,[23] contusions,[24,25] and drugs,[12] as well as coronary arteriosclerosis, the most common.[18-21] In 100 instances of complete right bundle branch block and 102 instances of incomplete right bundle branch block which included transient bundle block, eleven and sixteen different diseases, respectively, were observed.[26] The severity and extent of involvement of the heart and bundle branch tissue undoubtedly vary considerably in the different cases, and often no pathology is clinically demonstrable.[27] It has been suggested that in nonpermanent bundle branch block complete blockage of the bundle branch has not occurred, and the lesion is apt to be more focal.[16] The progressive nature of most cardiac disease and in particular of coronary arteriosclerosis would imply that over a period of years increasing changes in the conducting tissues would result in permanent bundle branch block.[18] This has usually been the case,[29-32] and transient block has been referred to as often the harbinger of permanent block.[15] Reversion from

bundle branch block to permanent normal conduction occurs occasionally. As in the first case of transient bundle branch block reported (Lewis, 1913),[33] the block is brought on by some acute illness, by infection, anemia, coronary alteration, or myocardial infarction, etc. The block disappears when the acute condition improves. It is unusual for bundle branch block of long duration, more than one year, to disappear permanently with return to normal conduction. However, a small number of cases of this type have been described. Kalett[34] in 1945 emphasized the rarity of such a condition and, in reporting a case, stated that Dr. Paul White, Boston, Mass., and Dr. H. M. Marvin, New Haven, Conn., wrote in personal communications that they had no knowledge of any such case previously where the electrocardiogram returned to normal after years of constant bundle branch block. In his case normal conduction was recorded four years after complete left bundle branch block had been noted, the block being present in all the intervening tracings. Myre and Fuller,[35] in June, 1951, reported a second such case of spontaneous reversion of left bundle branch block to normal after the block had been established for a long time (three years). They did not accept the idea of ". . . tissue anoxia sufficient to cause the depression of conductivity for three or more years, with retention of viability over the entire period which would enable the conduction tissue to regain function once the tissue anoxia was overcome by the development of sufficient collateral circulation."[35] As these authors were reluctant to consider this retention of viability for a three-year period, it is most unlikely that the damaged conduction tissue would remain viable over a period of ten years, then heal and resume its function of conduction. Since repair of the bundle of His when once destroyed probably does not occur,[36] and since specific muscle conduction is auxomerous,[37] that is, the excitation wave can be normally conducted as long as one fiber remains intact, the following hypothesis can explain unstable bundle branch block of long duration and probably other forms of nonpermanent bundle branch block, particularly those of long duration. After disease or injury involving the bundle of His and its main branches, the destroyed fibers and those severely damaged for a long period of time probably never recover to carry on the function of conduction. A few fibers remain intact. These will conduct the excitation impulse normally under favorable circumstances, but some local and often very slight change of circulatory, nervous, or chemical nature, not yet clearly understood, may result in the failure of these few remaining fibers to function. This has been postulated for atrioventricular block by Carter and Dieuaide.[38] It has been demonstrated experimentally by Baschmakoff[39] in his bridge experiment on the frog's heart. Variation in cardiac rate is a simple and common way of providing a suitable local alteration. The mechanism of an underlying pathologic disturbance with a superimposed precipitating or trigger factor, the latter frequently a change in rate, provides a satisfactory explanation for the entire group of intermittent, recurrent, and unstable bundle branch block—a group referred to as homogeneous.[30] Though the classical concept of the bundle branch system has been recently confirmed,[41-43] the above explanation is also not out of line with other concepts of the system of ventricular conduction and bundle branch block such as that of the Glomset and Birge,[44] and that of Segers[45]—peripheral block at the Purkinje-myocardial level.

In the case reported above, it is postulated that there occurred a post-wall myocardial infarction, due to changes in the coronary arteries which also involved the blood supply to the right bundle branch (ramus limbi dextri). This caused damage without complete destruction of the right bundle branch, leaving one or a few fibers intact. Conduction was precarious but was carried out normally under favorable conditions; a state of unstable bundle branch block existed, governed by a critical cardiac rate, frequently about 71 to 77 per minute. This unstable state of conduction in the right bundle branch persisted for ten and one-half years.

SUMMARY AND CONCLUSION

A case of unstable bundle branch block with changes in conduction induced by changes in cardiac rate when the heart was beating at a critical rate was described, lasting over a period of ten and one-half years. This is the longest such case on record.

The mechanism of unstable bundle branch block is discussed.

It is suggested that the mechanism may be the same in other forms of non-permanent bundle branch block, especially those of long duration.

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THE VENOUS VALVE IN THE AGED

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SYSTEMATIC studies of vein valves in general are very rare and there are no references in the more recent literature. We became interested in the vein valve because of finding inflammatory changes therein in instances of valvular endocarditis.[1] Because of certain changes which were interpreted as the result of old valvulitis, the question was raised as to whether or not such changes might be the result of the normal aging process. For that reason it was thought of interest to investigate the histologic appearance of the venous valve at various ages.

MATERIALS AND METHODS

A venous valve in the upper part of the femoral vein between Poupart's ligament and the entrance of the vena profunda was studied in individuals of the following ages: 41, 46, 49, 54, 61, 65, 67, 78, and 81 years. The appearance of this valve in the younger age groups was previously discussed.[1] None of the patients of either group had valvular endocardial lesions, nor clinical or pathologic evidence of increased venous pressure.

The valves were preserved in toto in 10 per cent solution of Formalin. Several blocks were cut from each valve either longitudinally or horizontally and imbedded in paraffin. In some instances serial sections were cut from the entire valve and in others only various numbers from each block. Every third section was stained with alum hematoxylin (or iron hematoxylin) and eosin, orcein, and according to the van Gieson method.

GROSS AND MICROSCOPIC APPEARANCE OF THE VENOUS VALVE

The normal gross and microscopic appearance of the valve has been given elsewhere.[1] The following may be recalled for the better understanding of subsequent changes: The valve consists of two cusps which spring from the wall of the vein very close to each other, their free margins diverging to become attached again at the opposite region of the wall of the vein. The space between the attach-

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ment of the free margins of the cusps is called the commissure. The commissure itself is slightly raised because of a thickening of the vein wall in that area. This projection is named "commissural mound" or "pedestal." The cusps are thicker at their bases, where they join the wall of the vein. This thickened attachment of the cusp framework is called "agger" (Franklin[2]), "limbus," or "tuberculum." The continuations of the free border of the cusp where it meets the vein wall are named cornua.

Microscopically, the cusp may be arbitrarily divided into two zones, a luminalis and parietalis (Fig. 1). The luminalis, that part of the cusp close to the lumen of the vein and facing the circulating blood stream, is lined by one layer of endothelial cells which are elongated in the axis of the vessel. Beneath this layer of endothelial cells is a small amount of connective tissue which is especially noticeable in childhood. Immediately beneath it there is a moderately thick, slightly wavy elastic lamella, the continuation of the internal elastic lamella of the intima

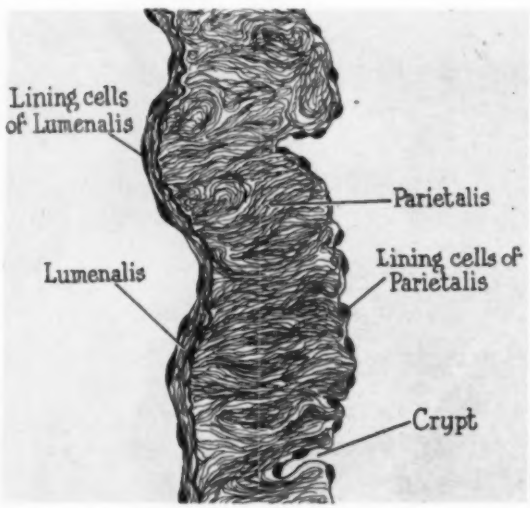

Fig. 1.

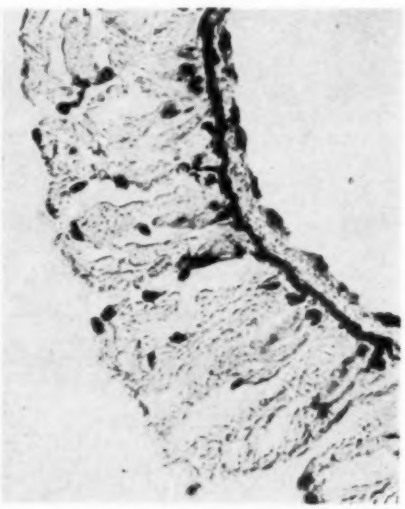

Fig. 2.

Fig. 1.—Schematic drawing of microscopic appearance of femoral vein valve giving the pertinent nomenclature. (Similar picture as used in Arch. Path.)

Fig. 2.—Valve of vein in child. Orcein preparation. × 280. (Similar picture as used in Arch. Path.).

of the vein (Fig. 2). Occasionally minute elastic fibers branch off into the adjacent collagen tissue of the parietalis. However, this is not the rule, though probably not pathologic. The parietalis, that part of the cusp facing the vein wall of the sinus, is lined by one layer of endothelial cells which are elongated transversely. A few minute crypts or crevices lined by endothelium face the sinus. These crypts are found in irregular intervals. Their bases occasionally reach the elastic lamella of the luminalis. The remainder of the parietalis, in general, consists of loosely arranged collagen fibers which appear the more lacelike the farther away they are from the base and the attachments to the vein wall. A connective tissue cell is occasionally present. At the base of the valve the parietalis contains also a few muscle fibers which extend from the longitudinal muscle layer of the vein wall.

These are present only in about the lower fifth of the cusp. There are no blood vessels in the cusps.

The luminalis and parietalis join or fuse at the distal end of the cusp, which is thinner than the rest. The elastic lamella there is also thinner than elsewhere and sometimes barely perceptible. The lacy collagen is correspondingly thin and the lining endothelial cells of the luminalis and parietalis are in close approximation.

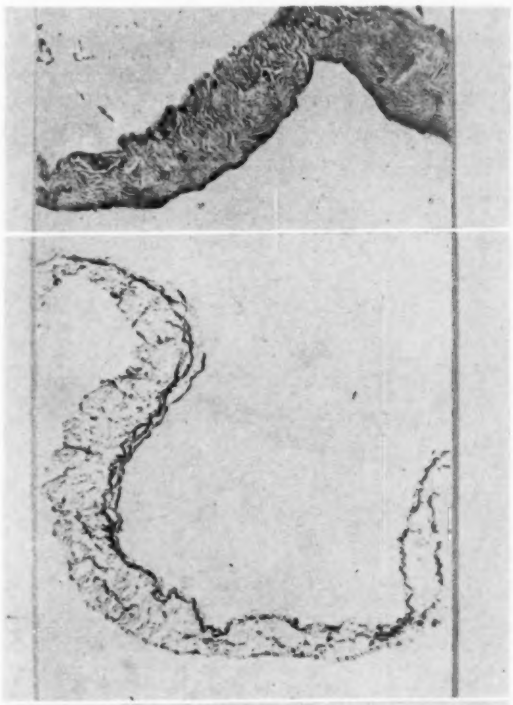

Fig. 3.

Fig. 4.

Fig. 5.

Fig. 3.—Fibrosis of cusp. (Patient aged 67 years). Hematoxylin-eosin preparation. × 140.

Fig. 4.—Note newly formed elastic lamellae arranged roughly parallel to elastica. • There are also a few thin elastic lamellae within parietalis. (Patient aged 54 years). Orcein preparation. × 140.

Fig. 5.—Note the connective tissue between the elastica and lining endothelial cells of the luminalis. (Patient aged 67 years). Iron, hematoxylin, and eosin preparation. × 140.

CHANGES WITH INCREASING AGE

With increasing age changes occur in the valve cusp in both layers, — the parietalis and luminalis.

Changes in the Parietalis.—The lacelike thin areolar tissue is gradually replaced by a thick dense collagen (Fig. 3). This transformation apparently occurs gradu-

ally, starting after the age of 30. There are no cellular elements or anything resembling new blood vessels. The crypts of the parietalis tend to become shallower and with advancing age seem much less noticeable. While normally in the younger age group a thin elastic fiber only rarely traverses the parietalis, elastic lamellae in later years appear here and there and increase gradually in number, starting in about the fourth decade. These fibers seem to constitute processes extending from the elastic membrane of the luminalis (Fig. 4). Gradually the elastic lamellae increase slightly in thickness and reach the base of some of the crypts or the region of the lining cells of the parietalis. Never have we encountered an extensive or more massive new formation of elastic elements. They are at first slightly more numerous at the base of the cusp, usually sparing the free margin. Only in the valve cusp of the 81-year-old patient did we encounter a considerable number of elastic lamellae at the free margin.

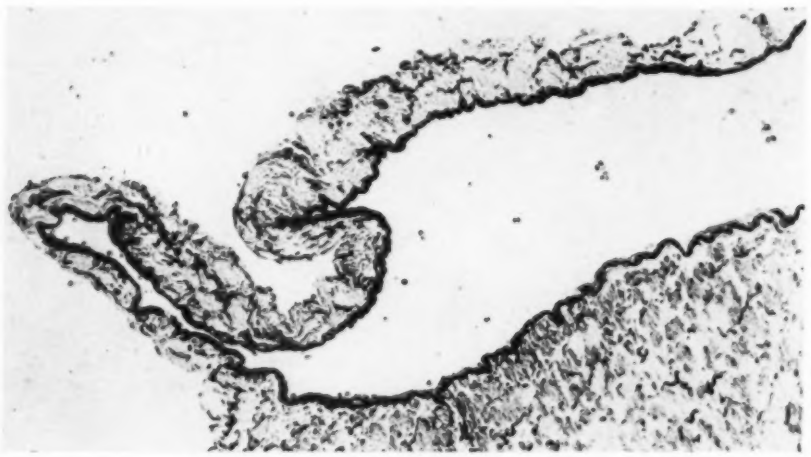

Fig. 6.—Note the "heavy" elastica and the thickened parietalis with elastic lamellae. (Patient aged 67 years.) Orcein preparation. × 140.

Changes in the Luminalis.—In the younger age group a very small amount of connective tissue is found between the lining cells and the elastic membrane of the luminalis. This is more pronounced in the first decade. Later it becomes barely perceptible. It is however again clearly visible after the age of 40 (Fig. 5). In the sixth decade and later there is usually an extension of a newly formed subintimal connective tissue from the vein wall just beneath the cusp into the cusp itself, located between the lining cells and elastica. It may extend upward into the proximal third of the cusp. This process is obviously an extension of increased endophlebohypertrophy[3] of the vein into the cusp and will be referred to below.

The elastica itself becomes thicker in the aged (Fig. 6). While in the younger age group the elastic membrane on low magnification appears as a more or less straight line, it shows a number of indentations in later years. Some of these, particularly those close to the base of the valve, are deep, pulling with them the lining endothelial cells. Thus, the luminalis may show a number of deep and narrow depressions comparable to fjords on a rugged coast line (Fig. 7). Besides the

thickening of the elastic membrane, there is a new formation of thin elastic lamellae, arranged more or less parallel to the elastica (Fig. 4). These changes may be noted already at the age of between 30 and 40. In one instance (81 years) a peculiar cystlike structure was found in the luminalis, between the elastica and the lining cells (Fig. 8). It projected into the lumen. In one area it seems as if it were subdivided by old connective tissue into two compartments. It was partly surrounded by collagen fibers. This cystlike space contained red blood corpuscles and could be compared with the so-called blood cysts found occasionally on the heart valve of the newborn infant.

Not all changes mentioned were present in every instance; sometimes the luminalis presented only slight deviations from the normal; or only one of the changes mentioned was present, while others were entirely absent.

Fig. 7.

Fig. 8.

Fig. 7. Note the thick elastica and the "fjord formation." (Patient aged 61 years.) Orcein preparation. × 100.

Fig. 8.—Note the "blood cyst" covered at one aspect by elastica of luminalis. (Patient aged 81 years.) Orcein preparation. × 70.

We have not observed blood vessels in the cusps of the venous valve.

To determine the presence of fat within the cusp in the older age group, selected cusps from cases other than those related here were submitted to frozen sections and stained for the presence of fat with Sudan III. In no case could fat globules be demonstrated.

Changes in the Vein Wall of the Sinus of the Valve.—With increasing age there seems to be more fatty tissue extending from the adventitia into the media of the vein wall (Fig. 9). Connective tissue and muscle fibers first seem to be spread by the fat tissue which later leads to atrophy and disappearance of these structures. This was more severe just proximal to the sinus than within the sinus itself. In the one 81-year-old patient, only a few thin longitudinal muscle fibers remained, some of which too were separated from one another by fat. There was no fat however between the intima and muscularis. In some instances increased endophlebohypertrophy and endophlebosclerosis were encountered in the intima.

Changes in the Vein Wall Just Distal to the Valve.—In the sixth, seventh, and eighth decades changes are seen in the intimal and subintimal layers of the vein just distal to the valve (Fig. 10). These are characterized by proliferation of subintimal connective tissue with a few elastic fibers. There is also a moderate increase in the inner musculature but the proliferation of the connective tissue

Fig. 9.

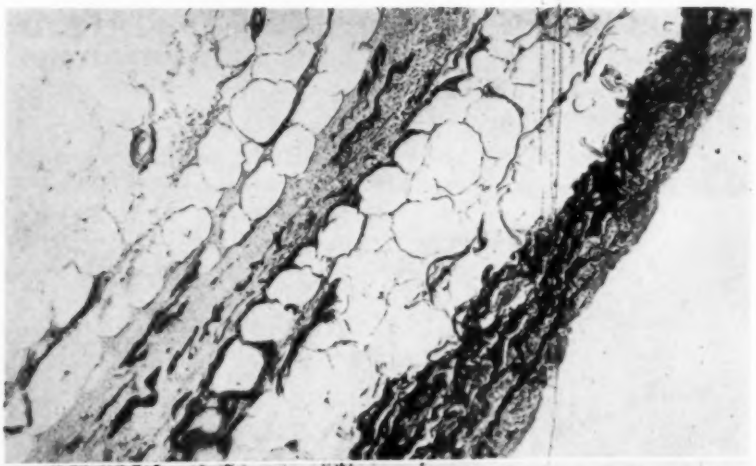

Fig. 10.

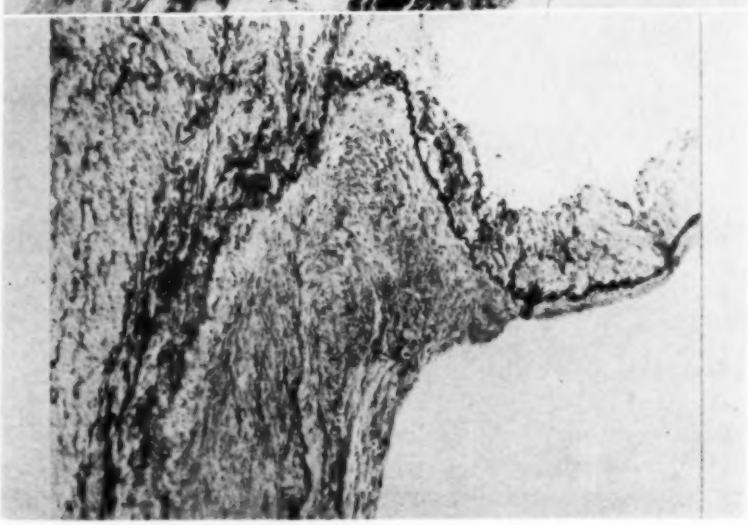

Fig. 9.—Vein wall in patient aged 81 years. Note the fatty infiltration. Orcein preparation. × 90.

Fig. 10.—Just beneath the valve there is severe "increased endophlebohypertrophy" which process extends into the luminalis of the cusp. (Patient aged 81 years.) Orcein preparation. × 120.

projecting into the lumen of the vein predominates the histologic picture. This process in the intima of the vein is similar to that described by us previously as endophlebohypertrophy, occurring normally with advancing age. This was considered a normal reaction of the vein to mechanical stress. However, the areas of thickening greatly exceeded that which might be expected normally. Thicken-

ing in excess, it was pointed out, was termed increased endophlebohypertrophy."[3] As mentioned before, the newly formed connective tissue also extended into the cusp itself where it was found in the luminalis between the lining cells and the elastica.

Thus, the more important changes in the venous valve occurring with advancing age are: (1) increase in (or the change from loose areolar connective tissue to) collagen, (2) new formation of thin elastic lamellae, (3) thickening of the elastica of the luminalis with apparent loss of elasticity as indicated by the "fjord" formation, (4) fat infiltration of the sinus wall of the vein, and (5) increased endophlebohypertrophy of the vein wall distal to the cusp.

INTERPRETATION OF FINDINGS

The replacement of the loose connective tissue of the cusp by collagen and the changes in the elastica seem to indicate that the cusp with increasing age becomes less flexible or movable than in the younger age group. Corroborating evidence for this assumption is the increased endophlebohypertrophy found just distal to the valve, this probably being caused by abnormal eddies brought about by an increasing, though obviously minimal, rigidity of the cusp. Thus this localized increased endophlebohypertrophy may be compared to the endocardial thickening occasionally found just beneath stenosed aortic valve orifices. While in the latter instances sometimes continuous eddies cause the formation of pockets (systolic pockets) such pockets were never found beneath the venous valve. However, such a pocket formation seems possible and special attention should be directed to this region in future cases in search of such a pocket.

While in the foregoing it was suggested that perhaps a minimal rigidity of the cusp may be responsible for abnormal eddies occurring just distal to the valve, with consequent increased endophlebohypertrophy, it might also be possible that a dilatation of the vein with age causing abnormal currents likewise may be accountable for this change. Whatever the cause may be, it seems that the final factor in the production of increased endophlebohypertrophy in this region is the occurrence of abnormal eddies.

Increased endophlebohypertrophy just distal to the valve was also encountered in instances of old (healed) venous valvulitis. The etiology of this condition in both instances seems identical. Newly formed collagen and thickened elastic lamellae were also encountered in these instances of healed venous valvulitis. However while in the latter instance there was also found an increase in cellular elements, such were not present in the valve of the aged. Also the wrinkling and "fjord" formation of the elastica were not found in the valves which were the seat of old valvulitis.

SUMMARY

With increasing age changes occur in the vein valve. The loose connective tissue gradually changes into collagen. There is a new formation of minute elastic fibers within the parietalis. The elastica of the luminalis becomes thicker

and new elastic lamellae are laid down parallel to the elastica. Endophlebohypertrophy present just distal to the valve extends from the intima of the vein into the luminalis of the valve. Increased endophlebohypertrophy is commonly encountered in this region and may be explained on the basis of abnormal eddies occurring in this area because of the thickening of the cusps of the valve.

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THE VALUE OF INTRAVENOUS PROCAINE AMIDE IN THE TREATMENT OF TACHYCARDIAS

Including Three Instances of Aberrant Ventricular Conduction Following Its Use

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TACHYCARDIAS can, under some circumstances, be considered cardiac emergencies. Any drug which can favorably influence an arrhythmia of this type is therapeutically a useful tool and deserves careful evaluation. Procaine amide, a monohydrochloride of p-amino-N-(2-diethylaminoethyl) benzamide, which has come into wide use during the past year appears to be the most promising drug for the treatment of tachycardias since the advent of Quinidine Sulfate.

The presently available literature,[1-4] would indicate that procaine amide is most useful in tachycardias of ventricular origin, of fair value in supraventricular tachycardias, and of no practical use in auricular fibrillation with or without rapid ventricular rates, except perhaps in fibrillation of short duration.

In the present study procaine amide was given twenty-two times to sixteen patients exhibiting tachycardias with successful results in fourteen instances.

The tachycardias were of various origin. Procaine amide was administered by the intravenous route solely, usually at a rate of 100 mg. per minute; an arbitrary limit of 1.0 Gm. was given at any one time. Blood pressure readings were taken at frequent intervals during the administration of the drug. Continuous tracings with a direct-writing electrocardiograph were recorded in most instances. Whenever possible, esophageal leads were taken during the study. This method insures more accuracy in determining the origin of the ectopic rhythm and facilitates observation of the atrial mechanism.

VENTRICULAR TACHYCARDIA

Five episodes of ventricular tachycardia occurring in four patients were treated with procaine amide. There was return to normal sinus rhythm in all instances. Small doses (300 mg.) were effective in all but one patient who required a total of 2.5 Gm. in divided doses. In one case the arrhythmia complicated a fresh subendocardial infarction. Another patient had developed a posterior myocardial infarction two months prior to the onset of the tachycardia.

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TABLE I. SUMMARY OF RESULTS WITH INTRAVENOUS PROCAINE AMIDE

CASE	HEART DISEASE	TYPE OF TACHYCARDIA	DOSE OF PROCAINE AMIDE	RESULT	COMMENT
1. J. B.	RHD	V	300 mg.	NSR	
2. M. H.	ASHD Subendocardial infarction	V	300 mg.	NSR	Tachycardia appeared a few days following the infarction
3. D. R.	ASHD	V V	300 mg. 350 mg.	NSR NSR	Treated on two occasions. Old posterior infarction
4. C. P.	ASHD	V	2.5 Gm. in divided doses	NSR	Gradual slowing of the ventricular rate from 190 to 130 followed by intermittent runs of sinus rhythm before complete return
5. A. G.	Normal	PAT PAT PAT PAT	800 mg. 700 mg. 600 mg. 700 mg.	NSR NSR NSR NSR	Cedilanid 0.8 mg. given on two occasions prior to procaine amide
6. A. C.	Normal	PAT PAT	700 mg. 700 mg.	NSR NSR	
7. S. J.	Normal	PAT	1.0 Gm.	Unchanged	Reverted with 1.0 Gm. of Quinidine Sulfate
8. C. C.	ASHD	Supraventricular with an arrhythmic ectopic focus	400 mg.	NSR	
9. A. B.	Tbc Pericarditis	Atrial	800 mg.	Slowing of auricular rate. Ectopic focus alternating with sinus node	Marked hypotension. Received digitalis following procaine amide. Sinus rhythm with second degree block appeared
	ASHD	Atrial	1.0 Gm.	NSR	Anterolateral infarction four weeks

10. G. T.	ASHD Myocardial infarction	Atrial	1.0 Gm.	NSR	Anterolateral infarction four weeks prior to onset of tachycardia
11. F. W.	ASHD	Atrial with 2:1 block	500 mg.	Slowing of auricular rate with increase in ventricular rate	Received digitalis subsequent to procaine amide. Developed auricular flutter
12. J. C.	ASHD	Atrial with 2:1 block	1.0 Gm.	Slowing of ventricular rate from 160 to 137 with persistence of 2:1 block	Mild hypotension
13. E. G.	ASHD Subendocardial infarction	Atrial fibrillation	400 mg.	NSR	Runs of aberrant ventricular conduction
14. S. S.	RHD Postmitral commissurotomy	Atrial fibrillation	1.0 Gm.	Auricular flutter with aberrant ventricular conduction	
15. T. O'T.	Peritonitis Heart normal	Atrial fibrillation with multifocal premature ventricular contractions	1.0 Gm.	Slowing of auricular rate	Subsequent development of auricular flutter
16. P. G.	ASHD	Atrial fibrillation	2.0 Gm.	No effect	

V = Ventricular.
PAT = Paroxysmal atrial tachycardia
NSR = Normal sinus rhythm.
ASHD = Arteriosclerotic heart disease.
RHD = Rheumatic heart disease.
Tbc. = Tuberculosis.

In Case 1 (Fig. 1) esophageal leads were available during the injection of procaine amide. The effect of the drug could be observed as the rates slowed independently. There was a 30 per cent slowing of the ventricular rate and a 23 per cent slowing of the atrial rate before reverting to normal sinus rhythm. With the return of normal rhythm, the sinus rate became that of the atrial rate immediately prior to the conversion.

SUPRAVENTRICULAR TACHYCARDIA

Eight patients were treated during twelve episodes of supraventricular tachycardia. On eight occasions normal rhythm followed intravenous procaine amide in four of the patients.

Three patients had paroxysmal atrial tachycardia. Two of these were treated successfully in six attacks. Case 5 (Fig. 2) illustrates the advantage of esophageal leads. The patient had paroxysmal atrial tachycardia with a left bundle branch block which when judged by routine electrocardiographic leads conceivably could have been misinterpreted as a ventricular tachycardia. The conduction defect did not prove to be any contraindication to procaine amide therapy as normal conduction returned simultaneously with conversion to normal rhythm. This patient was successfully treated on three subsequent occasions over a period of approximately one year for the same arrhythmia but with normal conduction (Fig. 3). Another patient, Case 6 (Fig. 4), with paroxysmal atrial tachycardia responded to the same dosage of procaine amide on two occasions.

Among those cases considered therapeutic failures was a patient whose ventricular rate slowed but whose ectopic focus in the atria continued to function partially by alternating with normal sinus beats.

Two cases of atrial tachycardia with 2:1 block showed slowing of the atrial rate. In one of these there was an increase in ventricular responses, some of which showed aberrant conduction (Case 11, Fig. 5). This type of arrhythmia is notoriously difficult to control with any form of medication.

ATRIAL FIBRILLATION WITH RAPID VENTRICULAR RATES

Atrial fibrillation with rapid ventricular responses is not usually thought of when discussing tachycardias, but it is so considered here since such a case frequently constitutes a cardiac emergency. There were no cases of the benign type of paroxysmal atrial fibrillation. The four cases treated in this study had fibrillation of recent onset. All were seriously ill at the time of treatment. In one, normal rhythm was restored. This was Case 13 (Fig. 5) in which atrial fibrillation complicated a fresh subendocardial infarction. While receiving procaine amide, long runs of aberrant ventricular conduction developed. In Case 14 (Fig. 6) aberrant ventricular conduction appeared in short runs during the administration of procaine amide, and after 1.0 Gm. had been given the aberrant conduction became continuous for fifteen minutes. After 0.8 mg. of Cedilanid had been given, carotid sinus pressure was applied and the rhythm changed to atrial flutter with a 2:1 block with normal ventricular complexes. The following day normal sinus rhythm was present. Procaine amide showed no apparent effect

during its administration to a patient with atrial fibrillation and multifocal ventricular complexes. However, four hours after treatment with both procaine amide and digitalis the patient developed an atrial flutter. It would seem unlikely that digitalis would change fibrillation to flutter, and in view of this development in this case as well as in Case 5, it is most probable that procaine amide was the influencing agent. We, as well as others, have observed coarse atrial fibrillation to develop into flutter in other instances.

The following cases are illustrative and bring out some unusual features:

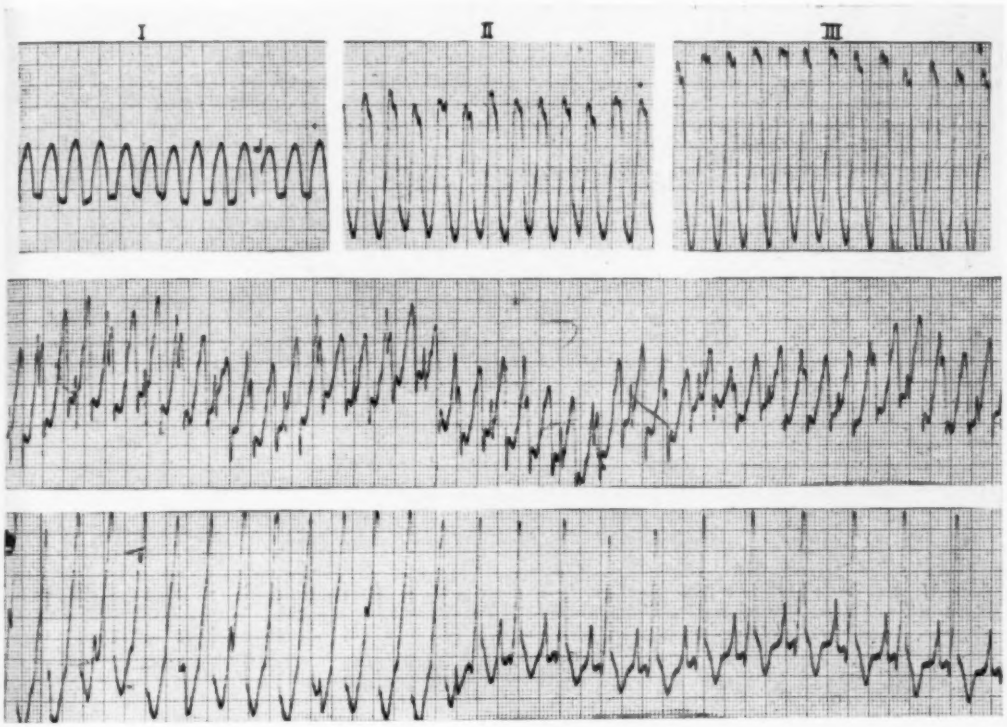

Fig. 1. (Case 1).—Ventricular tachycardia.
1, Leads I, II, and III.
2, Esophageal lead at atrial level before procaine amide.
3, Esophageal lead following 300 mg. of procaine amide showing reversion to normal sinus rhythm. Prior to treatment the atrial rate is 177 beats per minute and the ventricular rate is 268. These rates slow to 136 and 187 for the atria and ventricles, respectively, under therapy.

CASE 1.—J.B., a 31-year-old Negro man, was admitted on Sept. 26, 1950, with the chief complaints of palpitation and syncope. In the morning, before admission, the patient became dizzy, noticed palpitation and precordial pain followed by syncope which lasted approximately twenty minutes. Palpitation continued until the patient's admission.

Past history revealed that he had been hospitalized with rheumatic fever in 1943. The patient was hospitalized several times between 1943 and 1950. During this time he developed aortic and mitral lesions, an enlarged heart, and was subject to episodes of palpitation and syncope. On a previous admission to this hospital electrocardiographic evidence of ventricular tachycardia was obtained.

Physical examination on Sept. 26, 1950, showed cardiomegaly and aortic and mitral diastolic murmurs. At the time of admission an electrocardiogram showed a typical ventricular tachy-

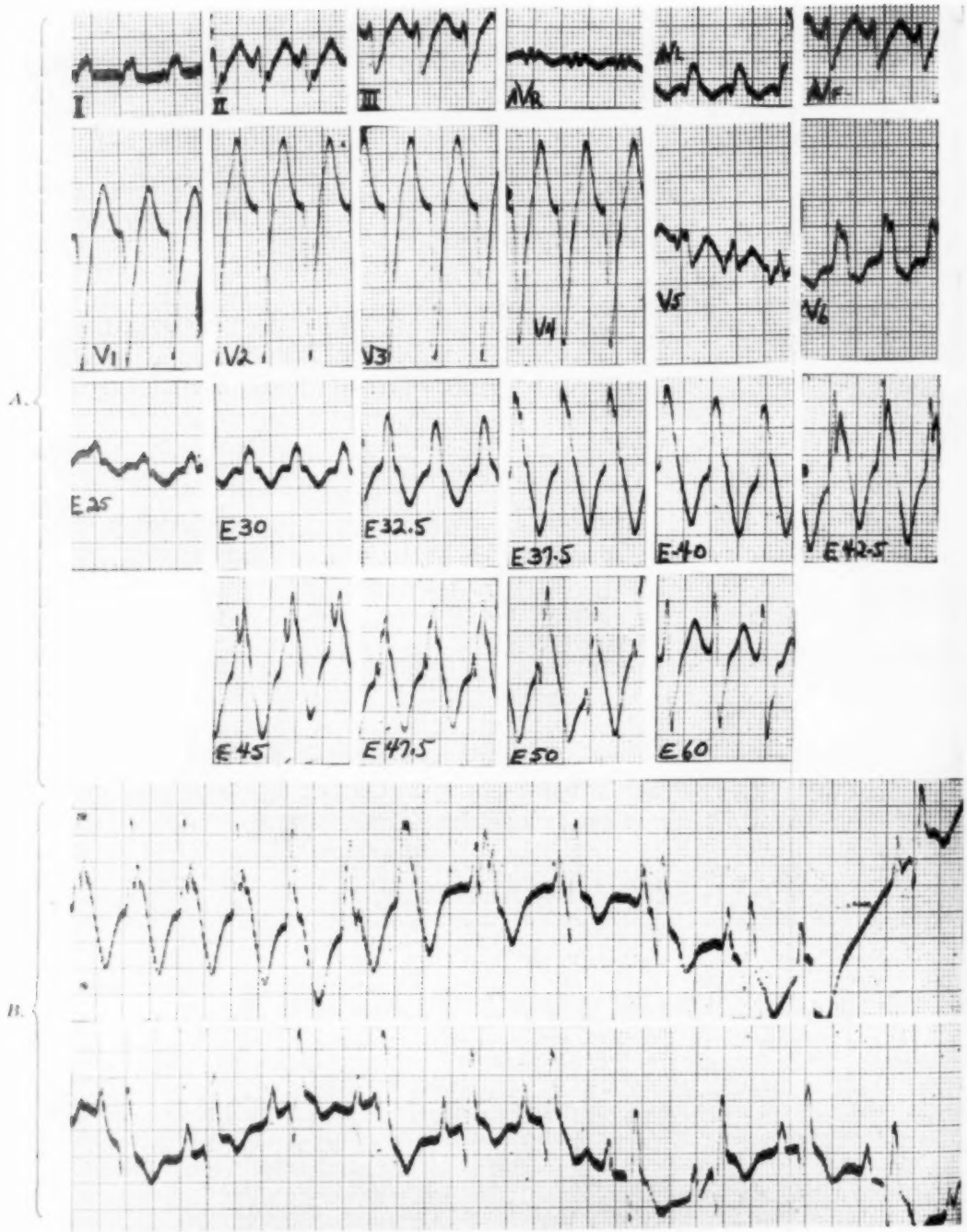

Fig. 2 (Case 5).—*A*, Supraventricular tachycardia with left bundle branch block with rate of 180 before receiving procaine amide. Conventional, unipolar, and esophageal leads.

B, After 700 mg. procaine amide. Rate was 150 immediately before conversion to normal sinus rhythm. Esophageal lead was approximately 42.5 cm. level continuous strip. P wave initiating ventricular complex in the tachycardia is found in the preceding QRS complex.

cardia with a rate of 260 (Fig. 1). Esophageal leads were recorded as intravenous procaine amide was administered. The control tracing showed an atrial rate of 177 and ventricular rate of 268. Following the injection of 300 mg. of the drug and immediately before conversion to normal sinus rhythm, the atrial rate had slowed to 136 and the ventricular to 187. While in the hospital on a maintenance dose of procaine amide, occasional extrasystoles were noted but there was no recurrence of the tachycardia.

CASE 5.—A.G., a 56-year-old white man, was admitted on Jan. 1, 1951, because of palpitation of sudden onset. He also noted a dull ache over the precordium and sternal area. He previously had approximately five episodes in the past twenty years, all of which stopped spontaneously within the period of a day. Physical examination showed him to be of unusual stature, standing 6 ft. 8½ in. tall, and weighing 168 pounds. Blood pressure was 130/80 mm. Hg. Other than rapid heart action and minor abnormalities, physical examination was essentially negative.

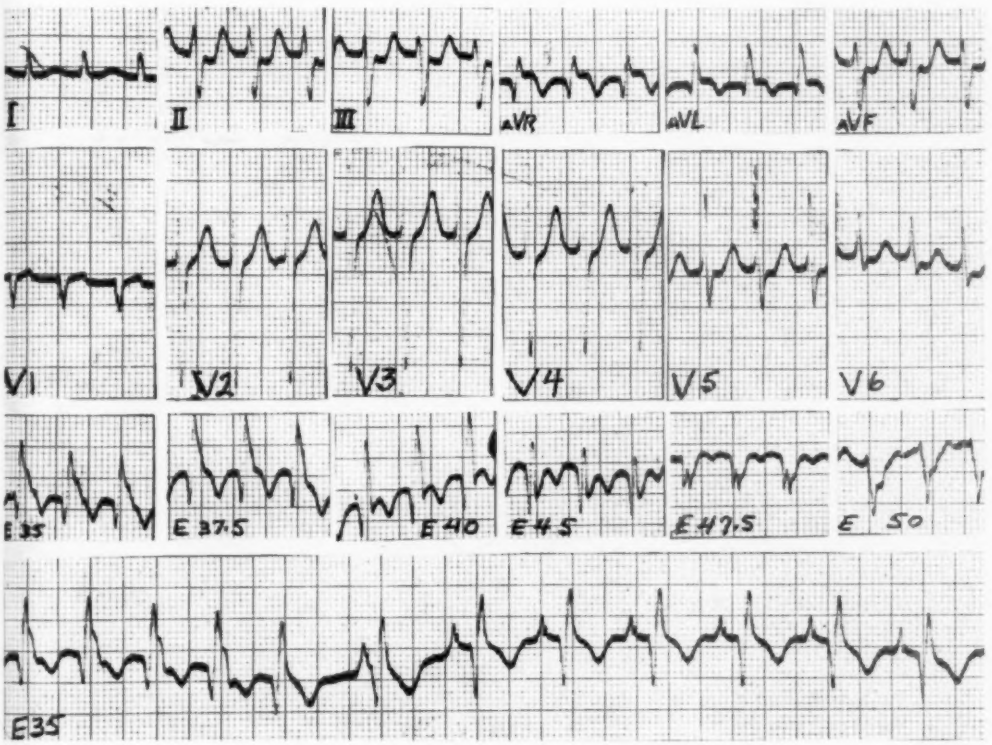

Fig. 3 (Case 5).—*A*, Supraventricular tachycardia with rate of 180. Esophageal lead markings are not accurate.

***B*, Following 800 mg. procaine amide rate has slowed to 150 immediately before abrupt change to normal sinus rhythm. Esophageal lead. The P wave initiating each ventricular complex in the tachycardia is found in the preceding QRS complex.**

An electrocardiogram showed what appeared to be either a ventricular tachycardia or a supraventricular tachycardia with left bundle branch block (Fig. 2). The rate was 180. Esophageal leads were taken and showed the left ventricular cavity potentials to be positive at the atrial levels. This finding suggested the diagnosis of left bundle branch block. P waves were discernible at esophageal levels 42.5 cm. through 50 cm. from nares, and fell within the QRS. After receiving 700 mg. of procaine amide normal sinus rhythm returned, and normal ventricular conduction appeared. The esophageal leads showed a complete reversal of polarity, lending support to the impression that conduction at the left bundle had been blocked during the tachycardia.

Second Admission.—The same patient was seen again Nov. 24, 1951, for a recurrence of palpitation of about five hours' duration. He complained of precordial distress. He had been free

from attacks for ten months. An electrocardiogram showed a typical supraventricular tachycardia at a rate of 180 (Fig. 3). With the esophageal lead in place and a continuous tracing being taken, procaine amide was given intravenously. The rate slowed gradually to 150 while 800 mg. was administered, following which normal sinus rhythm abruptly returned at a rate of 110. The sinus rate gradually slowed to 80 over the course of a few minutes. When 600 mg. had been received, the patient stated that the precordial distress had disappeared. An analysis of the electrocardiogram showed the P wave fell within the QRS. At the time of the termination of the tachycardia a QRS complex appeared without a superimposed P wave and the following complex was preceded by a P wave. Thus, each QRS complex in the tachycardia was initiated by the P wave appearing in the preceding QRS.

Fig. 4 (Case 6).—*1*, Supraventricular tachycardia. Esophageal lead at auricular level. Rate 154. *2* and *3*, 500 mg. procaine amide. Rate is 145 immediately before conversion to normal sinus rhythm. Continuous strip. P waves are superimposed on QRS complexes during the tachycardia and initiate the following ventricular complex. The P-R interval shows marked prolongation.

Third Admission.—The patient was seen again in the admitting office Dec. 16, 1951. His blood pressure was 90/60 mm. Hg. Because of the hypotension it was thought advisable to try rapid digitalization. Cedilanid 0.8 mg. was given intravenously without any change in the tachycardia but with a rise in blood pressure to 120/80 mm. Hg within a period of fifteen minutes. About one-half hour after the Cedilanid, 700 mg. of procaine amide was administered. The patient reverted to normal sinus rhythm. He was advised to use procaine amide orally to prevent further recurrence, but neglected to do so. Following an excess of alcohol intake Jan. 16, 1952 he again developed supraventricular tachycardia which responded to 600 mg. of procaine amide. The heart rate slowed from 170 to 130 during the injection before returning to normal sinus rhythm. Cedilanid 0.8 mg. was used prior to giving the procaine amide because of the hypotension and the blood pressure rose to normal levels and remained there. It is apparent that digitalis played no part in reversing the abnormal mechanism; since in all four instances the breaking point of the arrhythmia was produced with approximately the same amount of procaine amide.

CASE 6.—A.C., a 68-year-old white man, entered the hospital May 3, 1951, stating that he had had constant palpitation of the heart for five days prior to admission. Accompanying the palpitation there was a mild constrictive pain over the anterior chest wall. He had a previous history of similar episodes during the past three years accompanied by the same type of chest pain. Physical examination revealed only the presence of a tachycardia. The ventricular rate was 154. Esophageal leads were recorded but definite P waves were not seen (Fig. 4). However, the esophageal lead was placed at the atrial level and procaine amide was injected intravenously. As the medication was being given the atrial complexes became more apparent within the ventricular complex. Within seven minutes after the administration of 500 mg. procaine amide, the ventricular rate gradually slowed from 154 to 145. The arrhythmia changed abruptly at this dosage and this change was evident with a single ventricular complex appearing without a superimposed P wave. The following QRS complex was preceded by a tall positive P wave. Thus the QRS complexes occurring in the arrhythmia were initiated by P waves which appeared within the preceding QRS. The P-R interval was unusually prolonged. The patient was placed on oral Quinidine Sulfate 0.4 Gm. three times a day. Two days later there appeared a recurrence of the tachycardia. Once again esophageal leads were used while procaine amide was given. The same electrocardiographic observations were noted. Reversion to normal sinus rhythm appeared after 500 mg. of procaine amide. The patient was subsequently maintained on 250 mg. four times a day of oral procaine amide without recurrence of the arrhythmia.

CASE 11.—F.W., a 58-year-old Negro man, was admitted to the hospital April 26, 1951, because of dyspnea on exertion, edema of the lower extremities, and paroxysmal nocturnal dyspnea of several months' duration. On physical examination the patient was slightly orthopneic. Blood pressure was 130/80 mm. Hg. The heart was enlarged to percussion. The heart rate was 140. There were no murmurs. The liver was palpable one fingerbreadth below the right costal margin. There was 3 plus pitting edema of the lower extremities.

Roentgenogram of the chest showed the heart to be markedly enlarged. Electrocardiogram revealed an atrial tachycardia with 2:1 atrioventricular block with a ventricular rate of 150. Digitalization was used. The patient showed an excellent response in that he became edema free and no longer complained of dyspnea. However, the tachycardia persisted.

In an attempt to abolish the arrhythmia he was given procaine amide intravenously. While receiving the drug, the atrial rate slowed from 290 to 250, but the ventricular rate increased from 145 to 180, and the electrocardiogram showed a characteristic Wenckebach period (Fig. 5). With the development of a faster ventricular rate, procaine amide was discontinued after the patient had received 500 mg. It was noted that as the atrial rate slowed there were frequent aberrant ventricular contractions. Intravenous Digoxin 0.5 mg. was given and a reversal of the above patterns was seen. Following the Digoxin, carotid sinus pressure was applied with a resulting temporary prolongation of the atrioventricular block and a subsequent Wenckebach period. On the following day, there appeared a typical atrial flutter with a 3:1 and 2:1 block. Subsequently, the original electrocardiographic pattern again appeared.

On another occasion 1 Gm. Quinidine Sulfate was used. The response here was similar to that of procaine amide in that slowing of the atrial contractions occurred with the appearance of aberrant ventricular complexes. Further attempts to control the rapid ventricular rate by giving 1.6 mg. of Cedilanid in the face of complete digitalization resulted only in temporary increase of the atrioventricular block.

CASE 13.—E.G., a 58-year-old white man, was admitted to the hospital on June 4, 1951, because of substernal aching which radiated to his throat and right jaw. He was a known hypertensive individual for several years.

His blood pressure was 125/85 mm. Hg. Examination of his lungs showed moist râles and diminished breath sounds over the area of the right lower lobe posteriorly. There were no other significant findings on physical examination. Chest roentgenogram showed cardiac enlargement. On the second hospital day the white blood count was 10,200 with a moderate shift to the left in the neurophilic series. Sedimentation rate was 36 mm. per hour.

Electrocardiogram on admission showed atrial fibrillation with an intraventricular block and a ventricular rate of approximately 200. A few aberrant ventricular complexes were observed.

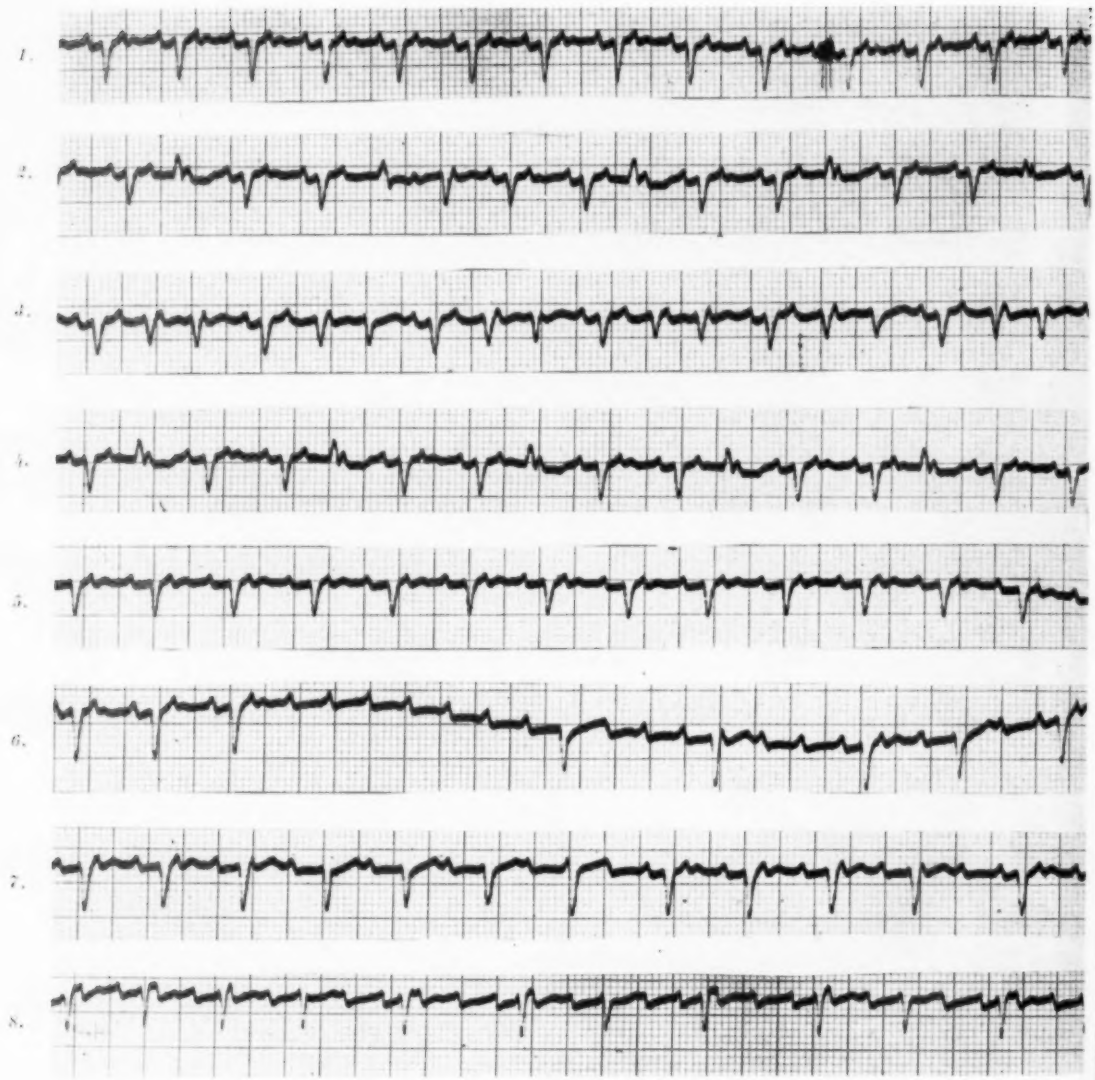

Fig. 5 (Case 11).—*1*, Control tracing Lead V_1. 2:1 atrioventricular block. (290-145)

2, After 200 mg. procaine amide the atrial rate was slowed to 273. The ventricle is responding more frequently and there are frequent aberrant ventricular contractions. Ventricular rate 160.

3, After 590 mg. procaine amide, atrial rate 250, ventricular 180. A Wenckebach period has developed.

4, After 0.5 mg. Digoxin given intravenously. Atrial rate 268, ventricular rate 160. Return of aberrant ventricular complexes and disappearance of Wenckebach period.

5, Following 1.0 mg. Digoxin. Atrial rate 268, ventricular rate 134. Tracing similar to control except that rate is slightly slower.

6, Right carotid sinus pressure.

7, Continuation of above tracing. Wenckebach period develops following carotid sinus pressure.

8, Taken the following day. Atrial flutter with 3:1 and 2:1 block. Auricular rate 283.

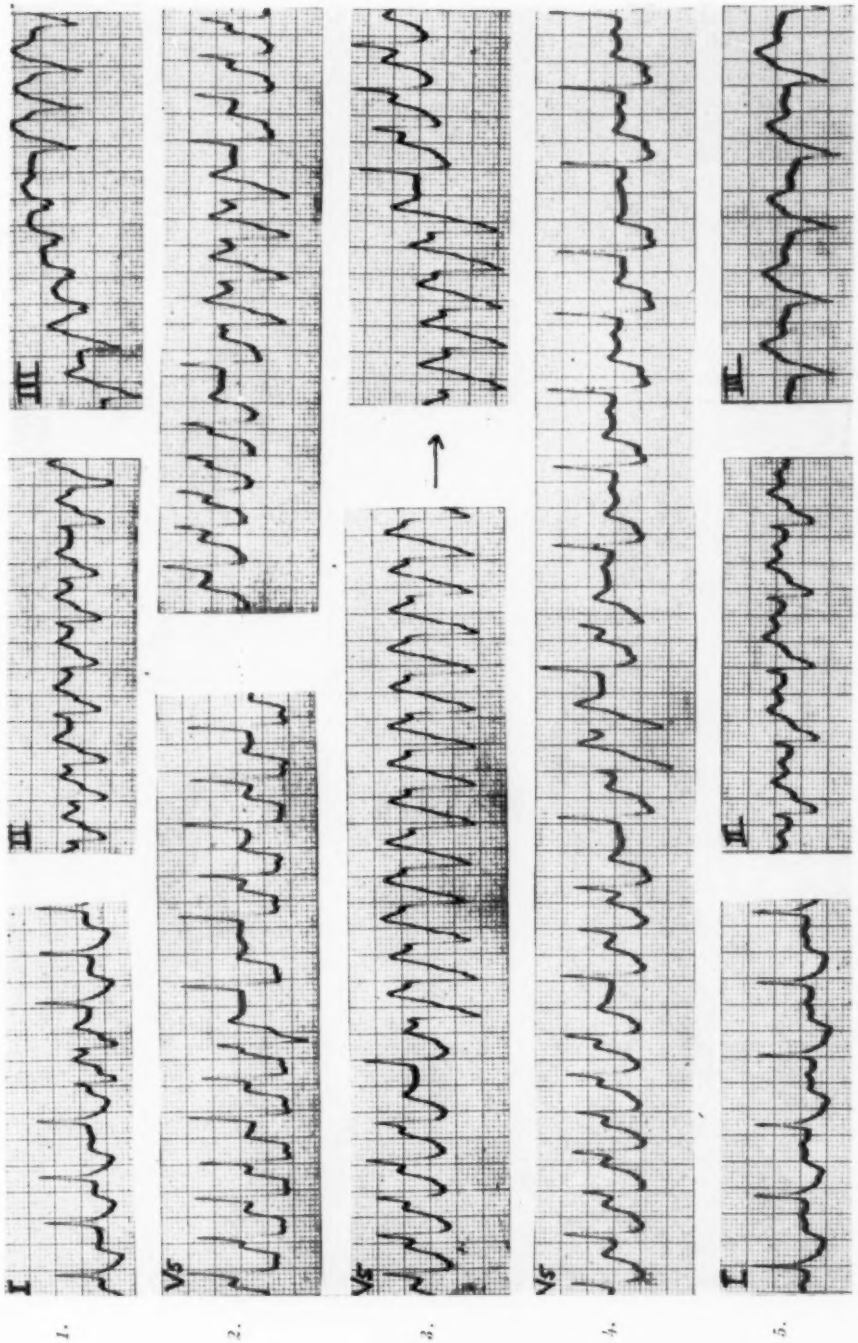

Fig. 6 (Case 13).—*1*, Atrial fibrillation with intraventricular block and a rapid ventricular rate. Leads I, II, and III.
2, Lead V_5 before and after 100 mg. of procaine amide.
3, 200 mg. of the drug. Arrow represents twenty-one seconds of aberrant ventricular conduction.
4, 400 mg. of procaine amide and conversion to normal sinus rhythm.
5, Leads I, II, and III immediately after.

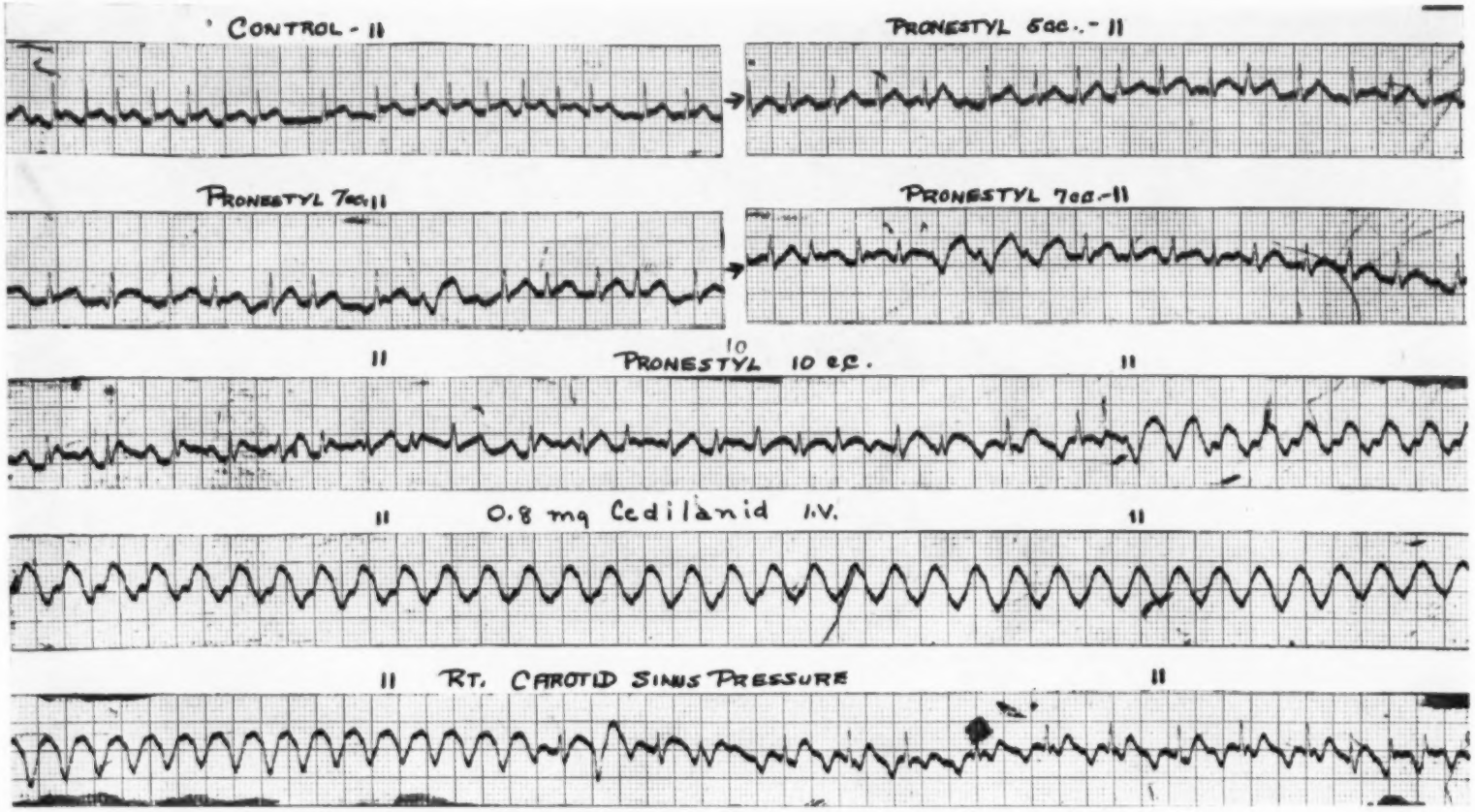

Fig. 7 (Case 14).—*1*, Atrial fibrillation with a ventricular rate of approximately 250. Gradual slowing of the ventricular responses and the development of aberrant conduction is seen while the patient received procaine amide.

2, Increase in the rate of aberrant ventricular conduction following 0.8 mg. Cedilanid to 250.

3, Normal ventricular conduction with atrial flutter at 2:1 ratio following right carotid sinus pressure. The ventricular rate is reduced by one-half to 125.

There was marked S-T depression in Leads I, II, aV_L and over the left precordium suggestive of subendocardial infarction.

The patient was given intravenous procaine amide at a slow rate. As the dosage increased, runs of aberrant ventricular complexes became more frequent and of longer duration (Fig. 6). There was a slight hypotensive effect. After receiving 400 mg. of the amide, normal sinus rhythm appeared. There was no further evidence of aberrant ventricular complexes.

The patient experienced an acute attack of pulmonary edema shortly after receiving procaine amide therapy. This was relieved by a bloodless phlebotomy and positive pressure oxygen. Following this the course was uneventful.

CASE 14.—S.S., a 44-year-old white man, was admitted to the hospital for consideration of a mitral commissurotomy. The patient's only symptom was dyspnea on exertion. The significant findings on examination were a typical mitral diastolic murmur, and enlargement of the left atrium by roentgenogram. The electrocardiogram showed an electrical axis of plus 60 degrees and a vertical heart. The operation which consisted of finger fracture of the stenotic mitral valve was uneventful. On the first postoperative day an electrocardiogram showed elevated S-T segments consistent with pericardial involvement. On the second postoperative day the patient noted a rapid heart rate. Electrocardiogram revealed an atrial fibrillation with a very rapid ventricular rate which at times was 250 (Fig. 7). As procaine amide was given there was a gradual slowing of the ventricular rate. There also appeared short runs of aberrant ventricular conduction (procaine amide 7 c.c.). At the completion of 1 Gm. of procaine amide a long run of rapid aberrant ventricular complexes at a rate of 214 ensued.

Intravenous Cedilanid was administered with an initial dose of 0.8 mg. The only change noted was a slight increase in rate, conceivably due to an increase in the atrial rate due to the Cedilanid. Carotid sinus pressure was then applied with a sudden cessation in the bizarre complexes and followed, after some initial irregularity, by an atrial flutter with a 2:1 block. The atrial rate was the same as that of the aberrant complexes both before and after the run of aberrant conduction. Further observation showed an occasional short reappearance of the aberrant ventricular complexes. Another 0.8 mg. of Cedilanid was given with the complete disappearance of aberrant complexes. Within the next twenty-four hours the patient reverted to normal sinus rhythm.

DISCUSSION

Our observations of the treatment of ventricular tachycardia with procaine amide indicate that this drug is highly effective. It is our opinion that this is the drug of choice in the management of tachycardias of ventricular origin. Quinidine Sulfate, while still a satisfactory drug in such instances, has several disadvantages. It cannot be given intravenously as safely as procaine amide. When given orally, there is considerable delay in achieving a therapeutic effect, which can be very important in ventricular tachycardias, especially when they complicate myocardial infarction.

Although we have treated too few cases of atrial tachycardia to warrant definite conclusions, it appears that procaine amide is an effective drug in the treatment of the usual forms of paroxysmal atrial tachycardia. In the other forms of supraventricular tachycardia the results were indifferent. There is probably no particular advantage in using procaine amide over other forms of therapy in paroxysmal atrial tachycardia other than for its more rapid action.

It appears desirable to digitalize any patient with atrial fibrillation with a rapid ventricular rate prior to treatment with procaine amide for the following reasons: (1) Procaine amide, like Quinidine Sulfate, produces a slowing of the atrial impulses which permits better atrioventricular conduction; when this occurs, the ventricular responses may increase. Further slowing of the atrial

mechanism may lead to atrial flutter which may also produce a rise in ventricular rate. (2) Frequently aberrant ventricular conduction, which can be confused with ventricular tachycardia, results from the treatment with procaine amide, as well as Quinidine Sulfate, when the ventricular rate increases. With digitalization, however, the ventricular rate is less likely to become more rapid as the atrial rate slows. This is due to the increase in atrioventricular block produced by digitalis. This has been the reasoning long since employed when using Quinidine Sulfate.

Two patients had intraventricular conduction defects concurrent with their tachycardias which was replaced by normal ventricular conduction when the arrhythmia was corrected. In a third patient both the tachycardia and conduction defect remained unchanged by treatment. Despite the fact that aberrant ventricular conduction does occur with procaine amide, intraventricular conduction defects do not appear to be an absolute contraindication to its use.

Procaine amide was used in this series on three patients with fresh to recent myocardial infarctions and two patients with old infarctions with no untoward effects.

Intravenous administration of procaine amide appears to be a safe procedure. The only practical disadvantage in its use by this route is its mild hypotensive action. It is of interest to note in Case 5 that Cedilanid on two occasions raised the blood pressure from hypotensive levels prior to administration of procaine amide to normal and apparently prevented any fall in blood pressure during subsequent injection.

SUMMARY

1. Procaine amide was given intravenously to sixteen patients during twenty-two episodes of tachycardia of various origins with conversion to normal sinus rhythm in fourteen instances.

2. Ventricular tachycardia was successfully treated in all of five attempts.

3. Supraventricular tachycardias responded in eight out of twelve episodes. Two cases of atrial tachycardia with 2:1 block included in this group did not revert to normal rhythm.

4. In four cases of recent atrial fibrillation with rapid ventricular rates, one returned to normal sinus rhythm and in two instances atrial flutter appeared.

5. Aberrant ventricular conduction at a rapid rate complicated two cases of atrial fibrillation. Isolated ventricular aberration appeared in one case of atrial tachycardia with 2:1 block when treated with both procaine amide and Quinidine Sulfate.

6. It would appear advisable to fully digitalize all patients with atrial fibrillation before giving procaine amide.

7. The intravenous route of administration is a safe method and results are accomplished rapidly.

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USE OF PENTAERYTHRITOL TETRANITRATE (PERITRATE)* IN TREATMENT OF ANGINA PECTORIS

Preliminary Report

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THE PRESENT study was undertaken in an effort to determine whether or not pentaerythritol tetranitrate (Peritrate) is effective in decreasing the severity and/or frequency of attacks of angina pectoris. The chemical formula and review of the drug's known physical and pharmacologic properties have recently been published by Winsor and Humphreys.[1] These authors reported a satisfactory decrease in the incidence of precordial pain in 78.4 per cent of patients with angina pectoris. Their results indicate that Peritrate was more effective in reducing the frequency of attacks than were placebos, Theocalcin, aminophylline, or khellin. Perlman[2] reported his results in eight patients with angina. Four of the eight patients received no relief, three patients received partial relief, and one patient obtained complete relief from anginal attacks on doses of Peritrate ranging from 30 to 160 mg. daily. Samuels and Padernacht[3] reported improvement in symptoms of intermittent claudication in twenty of thirty cases of arteriosclerosis obliterans treated with Peritrate. Our experience has been somewhat divergent from that of other investigators, and this preliminary report is being presented to stimulate further investigation of the drug, to determine its true value in the prophylaxis of angina.

Fourteen patients were selected from the Cardiac Clinic of the University of Arkansas School of Medicine and were followed for a long enough period to give valid observations. These patients had been under observation and treatment in the Cardiac Clinic for periods ranging from three months to four years prior to this study. Each patient had episodes of substernal pain or oppression, provoked either by exertion, emotion, overeating, or a combination of these three factors. These episodes of pain were relieved promptly by rest and/or nitroglycerin. Five of the patients also had hypertensive cardiovascular disease. The routine electrocardiogram was definitely abnormal in twelve of the fourteen patients. The two patients having normal standard electrocardiograms showed significant S-T segment changes following the Master two-step test. Ballistocardiograms were performed with Sanborn photoelectric ballistocardiograph on thirteen patients, using the technique of Dock and Taubman[4] modified by

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*Pentaerythritol tetranitrate (Peritrate) and placebos supplied by W. Strauss, M.D., Medical Director, Chilcott Laboratories, Division of The Maltine Company, Morris Plains, N. J.

Doherty,[5] and were abnormal in all cases (Table I). The two patients having normal standard electrocardiograms showed marked deviations from normal on their ballistocardiograms. We feel that with the clinical history, the electrocardiographic and ballistocardiographic findings, the diagnosis of angina pectoris was established beyond question in each case.

TABLE I. SUMMARY OF BALLISTOCARDIOGRAPHIC FINDINGS

CASE NO.	NORMAL	ABNORMAL*	I-J VARIATION	AMPLITUDE OF COMPLEXES	REMARKS
1	0	3	Marked	Normal to low	
2	0	2	Marked	Normal to low	
3	0	4	Marked	Low	
4	0	4	Marked	Low	
5	0	4	Marked	Low	Bizarre form
6	0	4	Marked	Normal to low	Confused pattern
7	0	4	Marked	Low	Confused pattern
8	0	4	Marked	Low	Late "M"
9	0	4	Marked	Normal	Bizarre form
10	0	4	Marked	Very low	Bizarre form
11	0	2	Marked	Normal	Tended to return toward normal during Peritrate therapy
12	0	4	Marked	Low	
13	0	4	Marked	Very low	Confused pattern. No change during Peritrate therapy

*Abnormalities graded as follows:
Grade 1 = Low amplitude only.
Grade 2 = Normal to low amplitude with alteration in form of complexes in resting or post-exercise tracing.
Grade 3 = Normal to low amplitude with alteration of form both in resting and postexercise tracings.
Grade 4 = No recognizable form.

Each patient was given a mimeographed sheet, one for each week, on which he was instructed to note the exact time of each episode of angina, and record whether the attack was relieved by rest or nitroglycerin. No change was made in the medications, such as digitalis, salicylates, phenobarbital, or nitroglycerin, which the patients were taking prior to the study. Each patient was observed for a control period of at least two weeks before instituting therapy with either Peritrate or a placebo. The patients were seen by the same observer at weekly intervals, or if they lived such a distance that weekly visits were impracticable they were seen at biweekly intervals. Eleven patients were started on Peritrate first, following the control period, and three were started on placebos first. The prophylactic effect of both Peritrate and a placebo was studied in thirteen patients. The placebo study in one patient (Case 8) was discarded because of addition during this period of another drug which might have relieved the attacks of angina. During the placebo period almost complete relief from anginal attacks was obtained, but it was felt the additional drug invalidated this period of study. Peritrate was administered in 10 mg. tablets, dosage being 10 to 20 mg. three times a day. The placebo closely resembled the Peritrate tablet but was not scored. Only one patient (Case 1) volunteered that there was a difference in appearance between the two tablets.

TABLE II. AVERAGE NUMBER OF ANGINAL EPISODES PER WEEK AND NITROGLYCERIN TABLETS USED DURING PERIOD OF CONTROL, PERITRATE 30 MG. DAILY, PERITRATE 60 MG. DAILY, AND PLACEBO ADMINISTRATION

CASE NO.	AGE (YRS.)	SEX	ETIOLOGY	A. CONTROL			B. PERITRATE 30 MG.			C. PERITRATE 60 MG.			D. PLACEBO		
				I	II	III	I	II	III	I	II	III	I	II	III
1	50	M	ASHD	2	14.0	10.0	6	11.5	7.5	8	13.2	7.7	8	14.3	7.2
2	60	F	HHD ASHD	2	13.0	6.5	6	9.7	6.1	3	9.3	6.0	8	7.8	5.1
3	71	F	ASHD	2	2.0	1.0	6	2.0	0.5	6	1.3	0.3	4	1.0	0.3
4	71	M	ASHD	2	3.0	3.0	2	2.5	0.5	8	0.9	0.9	4	0	0
5	58	M	ASHD	2	4.0	4.0	4	3.8	1.8	8	0.8	0.8	9	0.2	0.2
6	59	M	ASHD	2	12.5	6.0	—	—	—	4	9.8	4.3	1	10.0	4.0
7	60	M	ASHD	2	6.0	1.0	1	6.0	2.0	8	5.0	2.0	6	4.3	2.2
8	65	M	ASHD	2	8.0	1.0	6	11.7	2.7	2	7.0	3.0	—	—	—
9	46	M	ASHD	4	4.3	4.3	1	6.0	5.0	2	5.3	5.3	—	—	—
10	50	M	ASHD	3	5.7	0.5	—	—	—	7	3.1	1.1	4	1.5	0.5
11	65	F	HHD ASHD	2	2.5	0.5	15	0.3	0.2	—	—	—	4	0	0
12	56	M	HHD ASHD	4	13.8	11.5	—	—	—	4	14.5	5.5	3	12.0	5.5
13	61	M	HHD ASHD	3	8.3	0.6	4	5.5	0	—	—	—	5	3.2	0
14	52	M	HHD ASHD	4	8.0	6.0	4	7.8	6.5	4	8.2	5.3	6	7.7	5.5
Average per patient					7.5	4.4		6.1	3.0		6.5	3.5		5.2	2.5

HHD = Hypertensive heart disease.
ASHD = Arteriosclerotic heart disease.
Column I = Number of weeks of observation.
Column II = Average number of anginal episodes per week.
Column III = Average number of nitroglycerin tablets used per week.

RESULTS

Ten of eleven patients showed a decrease in number of anginal attacks while taking 30 mg. of Peritrate per day, as compared to the control period. Nine out of twelve showed improvement while taking 60 mg. of Peritrate daily as compared to their control period. However, eleven of the twelve patients who were given placebo showed an equal or more significant decrease in the average number of anginal attacks per week while taking the placebo tablet than while taking either dosage of Peritrate (Sections B and C, Column II, Table II). The mean number of attacks of angina per patient per week was 7.5 during the control period, 6.1 during the period of 30 mg. Peritrate daily, 6.5 during the period of 60 mg. daily, and 5.2 during the period of placebo administration.

Three patients did not receive 30 mg. Peritrate daily, two did not receive 60 mg. Peritrate daily, and two were not given the placebo. However, seven patients (Cases 1-5, 7, and 14) were observed during periods of both dosage schedules of Peritrate and the placebo. For this group of seven patients, the average number of anginal attacks per week during the control period was 7.1, during the period of 30 mg. Peritrate daily was 6.2, during the period of 60 mg. Peritrate daily was 5.5, and during the placebo period was 5.0.

By analysis of variance it was found that the difference between the control, treatment, and placebo periods would have to be 1.1 or greater to be significant. Thus, there is a significant difference in the number of attacks of angina per week when comparing either of the three treatment groups with the control group. There is no significant difference between the 30 mg. Peritrate daily period and the placebo period, but there is a significantly less average number of attacks per week during the placebo period as compared to the 60 mg. daily Peritrate period.

A similar comparison can be made in the number of nitroglycerin tablets taken during each period of the study (Sections A-D, Column III, Table II). It is seen here that the number of nitroglycerin tablets taken is less during the placebo period than in any of the other study periods. By statistical analysis it is found that a difference of 1.4 is necessary for significance. For comparison of these figures refer to Sections A-D, Column III, Table II.

Ballistocardiograms were obtained on Case 11 during the control period and later during therapy with Peritrate. The control tracing was abnormal, showing marked respiratory I-J variation with significant decrease in amplitude of the waves. The repeat ballistocardiogram during therapy showed disappearance of the previous I-J variation, and the only abnormality detected was a shortened K wave, sometimes seen on normal tracings.[6] It would appear that this indicates an improvement in the patient's ballistocardiogram during treatment with Peritrate (Fig. 1). Ballistocardiograms were obtained both before and during Peritrate therapy in only one other patient (Case 13) and no significant differences were noted in the two graphs (Fig. 2). It is interesting to note that these changes paralleled the clinical response in each case.[6] One patient (Case 11) became completely free of anginal attacks while taking Peritrate and one patient (Case 13) noted only slight decrease in the frequency and the severity of attacks while receiving the drug.

No toxic manifestations necessitating discontinuation of the drug were noted. However, three patients complained of mild insomnia during the first few days

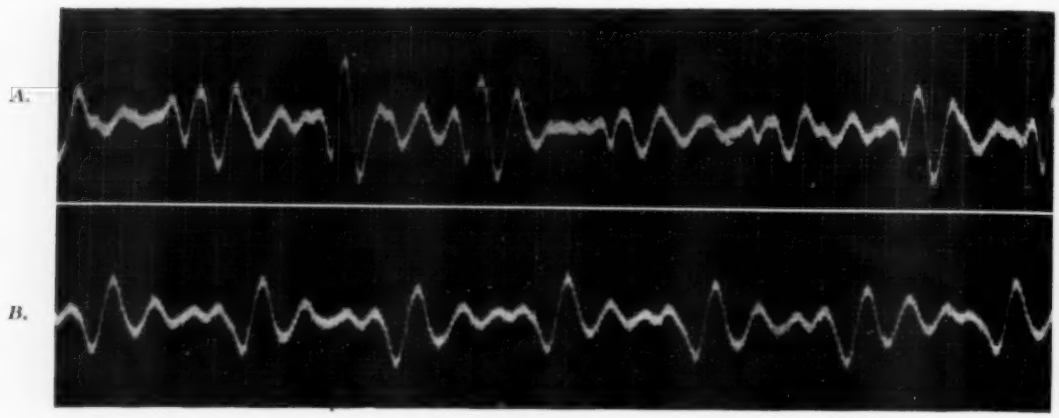

Fig. 1.—Ballistocardiographic tracings taken of Case 11. *A*, Before Peritrate therapy. *B*, During Peritrate therapy.

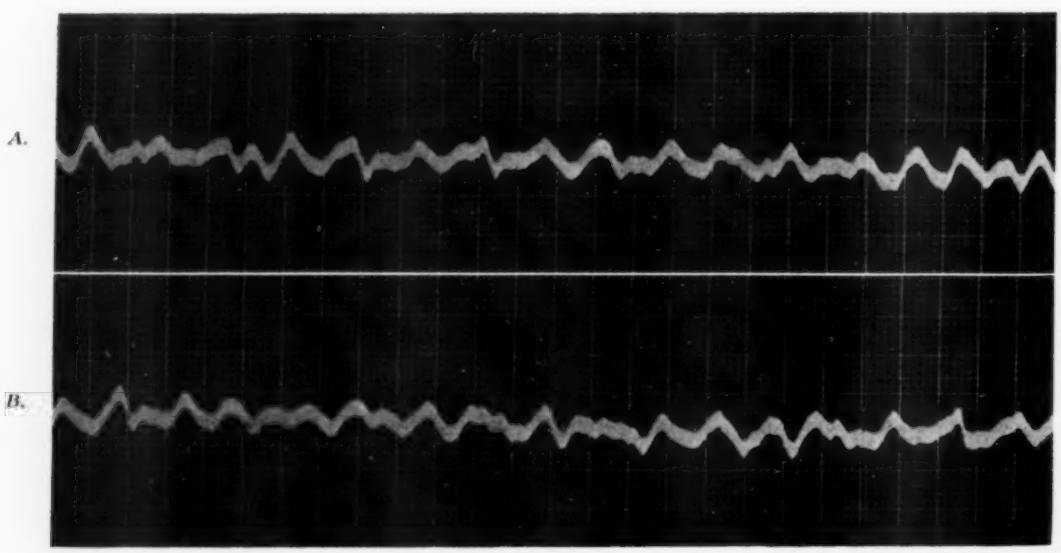

Fig. 2.—Ballistocardiographic tracings taken of Case 13. *A*, Before Peritrate therapy. *B*, During Peritrate therapy.

of therapy with Peritrate. One patient developed symptomatic postural hypotension while taking Peritrate. The drug was continued and the symptoms disappeared completely in about two weeks.

SUMMARY

1. Fourteen patients having symptoms of angina pectoris were studied to determine the possible effect of Peritrate in decreasing the number of attacks of angina.

2. The diagnosis in each case was established by the typical history and substantiated by abnormal ballistocardiograms in thirteen patients and abnormal electrocardiograms in twelve patients, and positive Master two-step test in the remaining two patients. A table of the ballistocardiographic abnormalities found is included. (Table I).

3. The patients were observed on two dosage schedules of Peritrate (30 mg. daily and 60 mg. daily), and on a placebo. The difference in response to these agents is discussed, and the results are analyzed statistically.

4. Similarly the number of nitroglycerin tablets taken per week was studied and analyzed.

CONCLUSION

Pentaerythritol tetranitrate (Peritrate) in dosages of 30 mg. daily and 60 mg. daily was not effective in reducing the number of attacks of angina when compared to a period of placebo administration.

The authors wish to express their appreciation to Dr. James S. Dinning, Department of Bio-Chemistry, for his assistance in computing the statistical analysis used in this study.

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A CALIBRATED BAR-MAGNET VELOCITY METER FOR USE IN BALLISTOCARDIOGRAPHY

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THE USE of various electrical transducers in the field of ballistocardiography has developed rapidly in the past few years. Along with the development of direct body pickups has been the growing awareness of clinicians of the lack of standardization of techniques and equipment. At the present time, it is extremely difficult to obtain any valid comparison of tracings since the amplitude and frequency response characteristics of all techniques have been as variable as the investigators. If this situation continues, research and development in this field will be open to much criticism and justly so. It is imperative that standardization of signal output be undertaken.

The standardization of absolute measurement of body motion has been attempted by a measurement of velocity because this minimizes the spread in measurements of the wave ratios among normal adults as compared to displacement and acceleration.[1] The width of the range encountered in body frequencies seems to affect velocity curves less than either displacement or acceleration. However, the standardization of absolute amplitude as well as of wave ratios is important, and it will be impossible to study the effects of resonance in relation to amplitude unless the signal output can be calibrated.

In order to be adequate for ballistocardiography, velocity measuring devices must have (1) no strong dependence on the initial relative position of the coil and magnet for the adjustment of sensitivity; (2) no extraneous signal from transverse motions, and (3) freedom from changes in output (such as are seen in pendulum attachments) due to variation in compliance (that is, constant response).

The bar-magnet velocity meter[2] fulfills the above condition and accurate calibration of velocity of body movement in units of millimeters per second can be developed. By the use of calibrated instrumentation, the first and most important step in direct ballistocardiography will have been completed. Research and development of clinical measuring techniques can then proceed on a quantitative basis.

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INSTRUMENTATION

The transducer used in these tests is a bar-magnet velocity meter. In essence this consists of a permanent bar magnet and an electromagnetic coil, free to move relative to each other. The coil follows the motion of the body, to which it is attached, and this motion with respect to the magnet (fixed in position) generates a voltage proportional to its velocity. (Equally well, the magnet could move with the body relative to a fixed coil.)

In detail, the velocity meter used in the preliminary tests described in this paper is a bar-magnet velocity meter consisting of a long Alnico V magnet and a long coil of wire. The coil is made from a commercial 1 lb., 4-inch spool of No. 32 single-silk enameled copper wire* in which the inside lead is brought out through

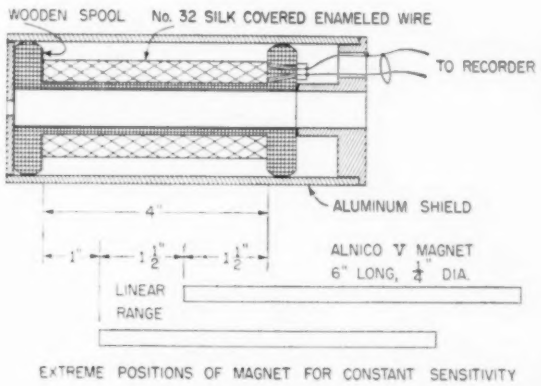

Fig. 1.—Schematic diagram and limits of linear range for ballistocardiograph bar-magnet velocity meter.

one end of a wooden spool. The magnet is a rod, 6 inches long and ¼ inch in diameter. Since the Alnico V material is not very strong in shear, it is preferable to enclose the magnet in a thin-walled tube of copper or brass. In order to shield the coil against 60 cycle and other pickup, it was found necessary to enclose the entire spool in an aluminum shield (Fig. 1). Tests showed that the range of relative positions of the coil and magnet over which the response is constant, within an accuracy of ±2.5 per cent, is about 1½ inch, as shown in Fig. 2. The frequency response of the velocity meter is flat within better than 1 per cent to above 100 cycles.

The ballistocardiograph records were taken with the subjects lying on a very rigid table (here made entirely of concrete and integral with the concrete floor). A clamping rod which serves as a support for the fixed element of the velocity meter (in this case, the magnet) was embedded in the table. The moving element

*Manufactured by New England Electrical Works, Inc., Lisbon, N. H.

(the shielded coil) was fastened to a wooden plank resting on the subject's legs just below the knees. The legs of the subject were supported only at the heels at a sufficient height to prevent contact between the calves and the table.

CALIBRATION

In order to obtain a calibration of the velocity meter, which would make possible the evaluation of the ballistocardiograph records in terms of amplitude of recorded velocity (in mm./sec., for example), the apparatus shown diagrammatically in Fig. 3 was used. (This calibration device is a modification of the

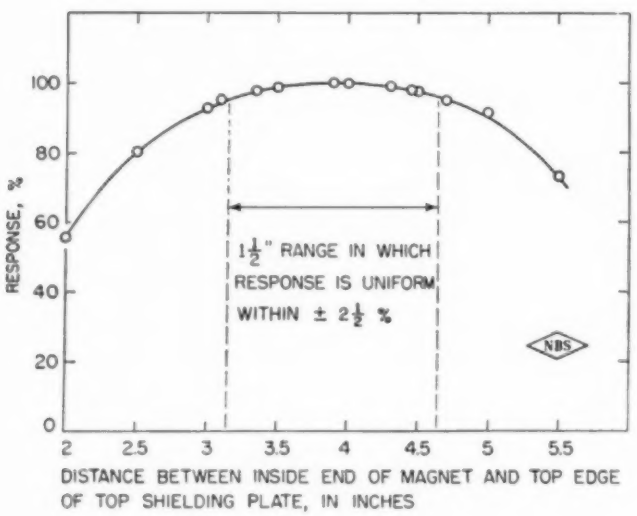

Fig. 2.

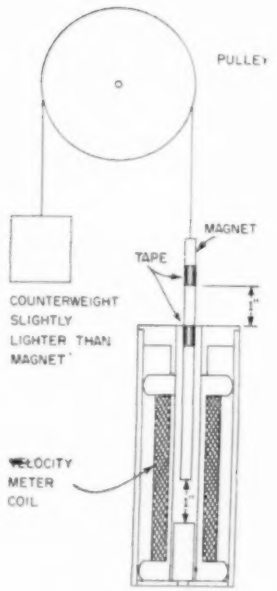

Fig. 3.

Fig. 2.—Chart showing sensitivity of bar-magnet velocity meter versus relative position of coil and magnet.

Fig. 3.—Schematic diagram of Atwood's machine calibration for bar-magnet velocity meter.

Atwood's machine used in physics laboratory demonstrations.) The magnet is nearly counterbalanced by a somewhat lighter weight, so that the entire system moves with a constant acceleration which is easily adjusted to any fraction of the acceleration due to gravity by changing the amount of unbalance. Such a system was necessary because the recorder could not follow the very rapid motion resulting when the magnet is simply dropped in free fall into the velocity-meter coil. By arranging a block at the lower end of the linear range of the bar-magnet velocity meter, and with two pieces of tape to show the desired total travel, it is easy to give the magnet an accurately known displacement with respect to the coil. A typical record of velocity versus time is shown in Fig. 4. Six successive 25-mm. calibrations made in this manner resulted in velocity-time traces, the areas under which agreed within ±2 per cent of the mean value (585 chart mm.^{2}).

A correction for amplifier low-frequency response (indicated in the figure) appears to amount to less than 2 per cent and has been neglected.

Let d = the total calibration displacement of the magnet, in mm.
A = the measured area in (chart mm.)²
s = the paper speed (time calibration) in chart mm. per second
x = the velocity calibration of body motion in mm./sec. per chart mm.

The total displacement *d* of the magnet relative to the coil is given by:

d = the integral of *velocity with respect* to *time.*

The right-hand side of this equation is proportional to the area under the calibration curve (Fig. 4). Then it follows that:

$$\text{d (mm.)} = \text{A (chart mm.)}^2 \cdot \text{x} \left(\frac{\text{mm./sec.}}{\text{chart mm.}} \right) \cdot \frac{1}{\text{s}} \left(\frac{\text{sec.}}{\text{chart mm.}} \right)$$

or:

$$\text{A (chart mm.)}^2 = \text{s} \left(\frac{\text{chart mm.}}{\text{sec.}} \right) \cdot \frac{1}{\text{x}} \left(\frac{\text{chart mm.}}{\text{mm./sec.}} \right) \cdot \text{d (mm.)}$$

and thus:

$$\text{x} = \frac{\text{sd}}{\text{A}} \quad \text{so, for s} = 50 \text{ (chart mm.)/sec.}$$

$$\text{x} = \frac{50 \text{ (chart mm.)/sec.} \times 25 \text{ mm.}}{585 \text{ (chart mm.)}^2} = 2.14 \text{ mm./sec. per chart mm.}$$

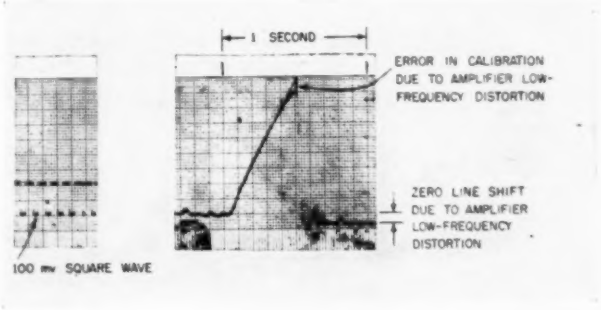
1 SECOND
ERROR IN CALIBRATION DUE TO AMPLIFIER LOW-FREQUENCY DISTORTION
ZERO LINE SHIFT DUE TO AMPLIFIER LOW-FREQUENCY DISTORTION
100 mv SQUARE WAVE

Fig. 4.—Calibration records: 100 millivolt square wave and Atwood's machine calibration of the bar-magnet velocity meter.

This calibration is for Channel A of a 4-channel Sanborn Poly-Viso recorder. By this method, at 1/100 of full gain, the sensitivity was found to be 2.14 mm./sec. per chart mm. At the sensitivity used for the ballistocardiographic records (¼ of full gain) the calibration was therefore 0.085 mm./sec. per chart mm.

This value was independently checked by another calibration method, and the agreement was well within the 5 per cent accuracy required for clinical applications.

A typical peak-to-peak velocity for the IJ wave (32 chart mm.) is shown in the labeled complex in Fig. 5, and thus represents 2.7 mm./sec. velocity. A

rough estimate of the associated peak-to-peak IJ displacement (obtained by dividing the above value by $2\pi f$, f = 5 C.P.S.) is about 0.1 mm. or 0.004 inch.

CASE REPORTS

CASE 1 (Fig. 5).—Velocity ballistocardiogram of a 30-year-old normal man. Channel A on Poly-Viso is calibrated at 0.085 mm./sec. per chart mm. The I-J segment represents a body velocity of 2.7 mm. per second.

CASE 2 (Fig. 6).—Velocity ballistocardiogram of a normal 48-year-old man. The peak-to-peak velocity of the I-J segment is calibrated at 0.085 mm. per second (Channel A) and represents a body velocity of 2.3 mm./second.

CASE 3 (Fig. 7).—Two cases of coronary heart disease.

A, The tracing of a 58-year-old man with a healed anterolateral wall infarct. No angina. The I-J segment represents a velocity of 0.43 mm. per second.

B, Tracing of a 54-year-old man with a healed posterior infarct. No angina. Wave segments are difficult to identify. The I-J segment represents a body velocity of 0.76 mm./second (Channel A).

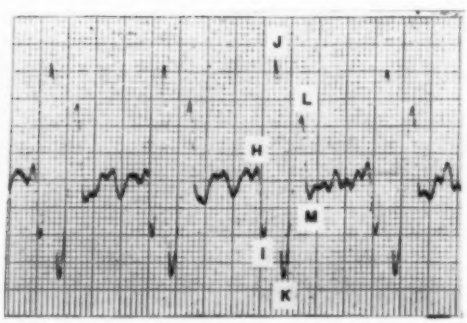

Fig. 5.

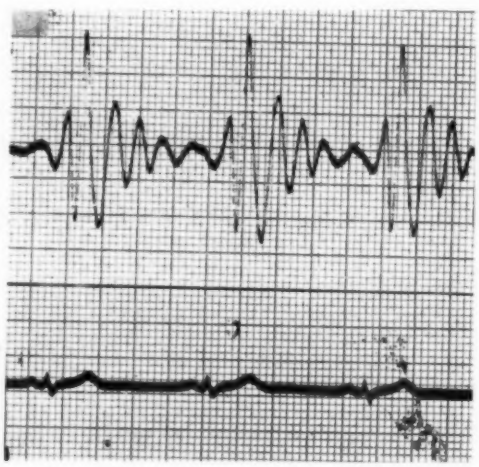

Fig. 6.

Fig. 5.—Velocity ballistocardiogram of a 30-year-old normal man.
Fig. 6.—Velocity ballistocardiogram of a normal 48-year-old man.

DISCUSSION

The use of calibrated instrumentation should be attempted in the development of ballistocardiography. With instruments such as the calibrated bar-magnet velocity meter, dependable correlation of amplitudes on inspiration and expiration can be obtained. Since the body is displaced as much as 0.005 inch during quiet respiration, many transducers used today will yield amplitudes of distorted values due to a lack of an acceptable range of linearity of output. This is especially true of some of the coil-and-magnet velocity measuring devices that are presently being used. The large range of constant sensitivity of the bar-magnet velocity meter is an advantage since adjustment does not have to be critical and inexperienced technicians can easily be taught to use this type of instrumentation.

There will be clinical value in the measurement of displacement and acceleration. This can be done best by starting with a velocity signal and integrating and differentiating the signal. To get adequate linearity of frequency response in the ranges of body motion, it is probable that a loss of signal up to 97 per cent may be necessary. To integrate or differentiate twice would entail amplification and expensive instrumentation. With the bar-magnet velocity meter it is possible to construct a model that will yield an adequate displacement and acceleration signal without additional amplification.[3]

In the future development of ballistocardiography there are many areas that need exploration and study. A study of various types of footrests is necessary. The weight of the platform placed on the legs should be investigated. The influence of the inherent frequency of the body mass as a spring-mass system should

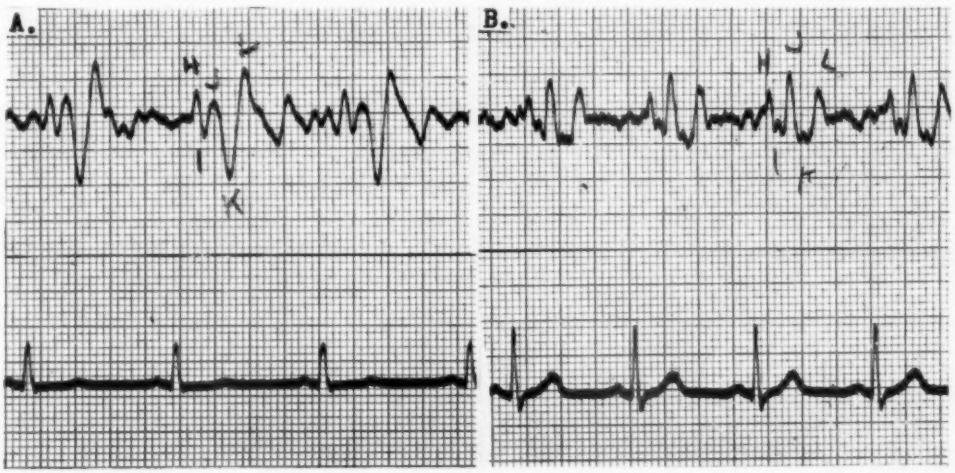

Fig. 7.—Two cases of coronary heart disease.

be investigated to show the effect on amplitude and wave contour. Values of amplitude in relation to inspiration, expiration, and other variables must be more clearly defined. The standardization of signal output and frequency response characteristics of the transducer are essential before adequate exploration of direct ballistocardiography can be attempted.

It has been suggested that velocity measuring devices could be calibrated so that 1.0 chart mm. of amplitude could represent 0.1 mm. per second velocity.[4] This is a convenient amplitude for clinical use, and the velocity of body motion could be easily translated into absolute units of mm./second. Thus, 2.0 cm. (20 mm.) of chart amplitude would represent 2.0 mm. per second velocity.

SUMMARY AND CONCLUSIONS

1. The construction and use of a calibrated bar-magnet velocity meter with a simple method of calibration has been described.

2. The value of standardized signal output in ballistocardiography has been emphasized; absolute body velocity can then be read directly from the recording.

Grateful acknowledgment is made to Thomas A. Perls, Ph.D., physicist, Office of Basic Instrumentation, National Bureau of Standards, who developed the instrumentation as well as the techniques used in this calibration; also to J. D. Garner, medical technician, for his assistance in calibration.

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A TEACHING AID FOR VISUALIZING THE DIRECTION OF ELECTRICAL FORCES OF THE HEART IN SPACE

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IT IS now obvious that the bipolar and unipolar extremity leads record from the same underlying electrical forces. There is considerable evidence indicating that the unipolar precordial leads are influenced mainly by the heart as a whole and therefore record from the same forces as do the extremity leads.[1] By studying the deflections recorded by electrodes in appropriate positions, one is able to determine the direction of electrical forces in space.[2] This is done as follows: (1) The vector representing the frontal plane projection of the electrical force of the QRS, S-T, or T is recorded on the triaxial reference system of Bayley. This is accomplished by inspecting the deflections of the three bipolar extremity leads and determining which lead has the largest deflection and which lead has the smallest deflection, utilizing the resultant area of each deflection to determine its relative size. The mean vector under study will be relatively parallel to the lead axis with the largest resultant deflection or perpendicular to the lead axis with the smallest resultant deflection, and its direction must satisfy the polarity of all three extremity leads. The axes of the augmented unipolar extremity leads can be superimposed on the triaxial reference system of Bayley to form a hexaxial reference system as shown in Fig. 3,*B*. By inspecting the augmented unipolar extremity leads in a manner similar to that described for the bipolar extremity leads, one can achieve increased accuracy. (2) After identifying the direction of the frontal plane projection of a spatial vector, one then locates the transitional complex of the precordial leads. The transitional complex is recorded along the transitional pathway, which is produced by an isopotential plane perpendicular to a spatial vector at its origin extended to intersect the surface of the chest. This plane, which is perpendicular to the spatial vector under study, will, therefore, determine the anterior or posterior displacement of a vector from the frontal plane, thus identifying its spatial position.

Because these spatial vectors are at times difficult to visualize, it seems desirable to illustrate them by a model. The model most useful in our hands is that shown in Fig. 1.

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The object of a model of this nature is to illustrate a vector and its perpendicular isopotential plane superimposed on the hexaxial reference system and

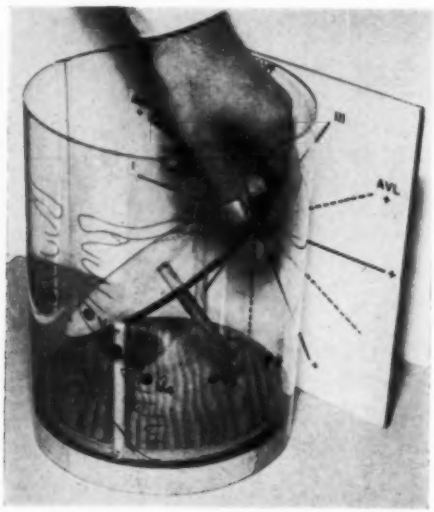

Fig. 1.

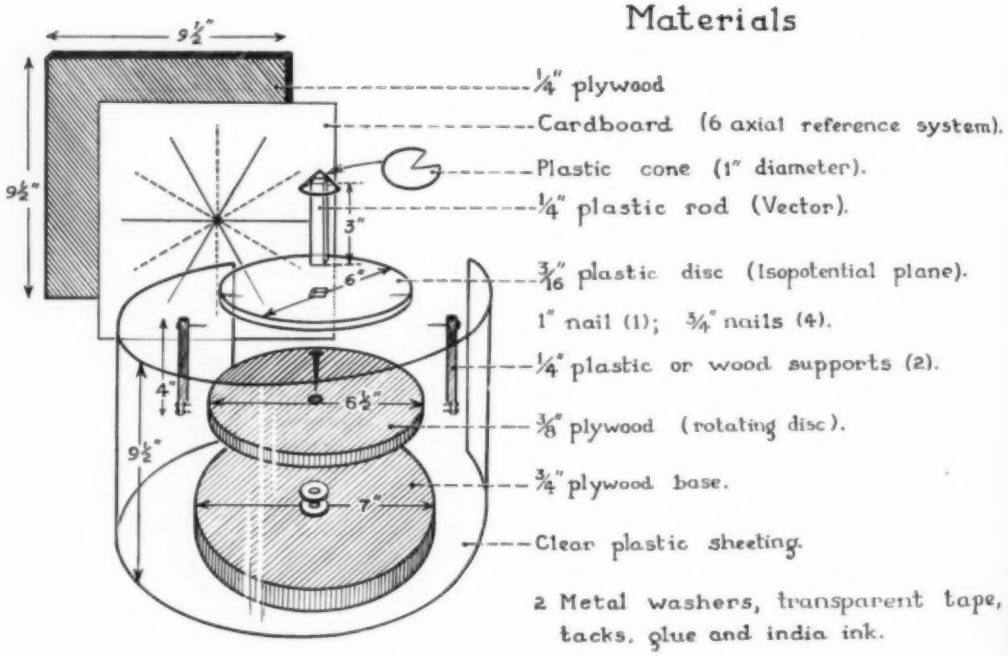

Fig. 2.

appropriately placed in an idealized cylindrical model of the chest which shows the conventional precordial electrode positions. The origin of electrical force varies in different subjects and is not located precisely in the center of the chest.

For simplicity, however, we have empirically placed the origin of electrical force 2 to 3 cm. below the V_1 and V_2 precordial electrode positions in the center of the chest and superimposed it on the exact center of the hexaxial reference system.

CONSTRUCTION

Attach the $\frac{3}{8}$-inch plywood disk to the $\frac{3}{4}$-inch wood base loosely with a 1-inch nail, 2 washers being imposed between the wood disks. Then nail the supports to the edge of the rotating plywood disk. The plastic rod (representing the vector) is fitted into a hole in the center of the plastic disk and must be exactly perpendicular to it (plastics are readily welded together with chloroform). Drill holes slightly smaller than the nails in both the disk and the supports, and nail the plastic disk to the upright supports so that the disk and vector assembly swing freely. Draw the outline of the chest and the chest electrode positions on the clear plastic sheeting with India ink and tack this around the base. Next draw the hexaxial reference system on cardboard and glue this to the piece of square plywood and nail to the back of the $\frac{3}{4}$-inch base so that the center of the hexaxial system, the origin of the vector, and a point on the chest just below and between leads V_1 and V_2 are superimposed when viewed from the front (Fig. 2). The vector tip is formed from a small disk of plastic sheeting from which a pie-shaped piece has been cut. By a combination of rotating the plywood disk at the base and swinging the plastic disk any vector position may be demonstrated.

In order to illustrate the usefulness of the model a tracing of a posterior myocardial infarction is shown in Fig. 3,*A*. Fig. 3,*B*, illustrates the frontal plane projection of the mean spatial QRS, 0.04, S-T, and T forces. Fig. 3,*C*, shows the spatial orientation of the vectors as determined by the location of the transitional pathway on the chest. This is an important step in visualizing the spatial direction of electrical forces, and one should be able to visualize such a figure without the use of a diagram. Unfortunately this step is frequently difficult for the beginner and it is for this reason that we have depicted the chest as a cylindrical volume conductor. To further clarify this confusing step we have shown diagrams of the model illustrating the various spatial forces in Fig. 3,*D*. The model has been found to simplify greatly the problem for the student in vector electrocardiography.

The model illustrated is an oversimplification of fact and it must be realized that it cannot represent precisely all vector positions for all electrocardiograms. The reason for this is threefold: (1) the origin of electrical forces is not centrally located and probably varies in different individuals; (2) the chest contour varies from subject to subject and this in turn alters the electrode positions, for example, in the long-chested individual, electrode positions V_2, V_3, and V_4 are almost in a vertical line while in the short stocky individual they tend to be more horizontally placed, and (3) technical error of precordial electrode placement will greatly alter the assumed location of the transitional complex.

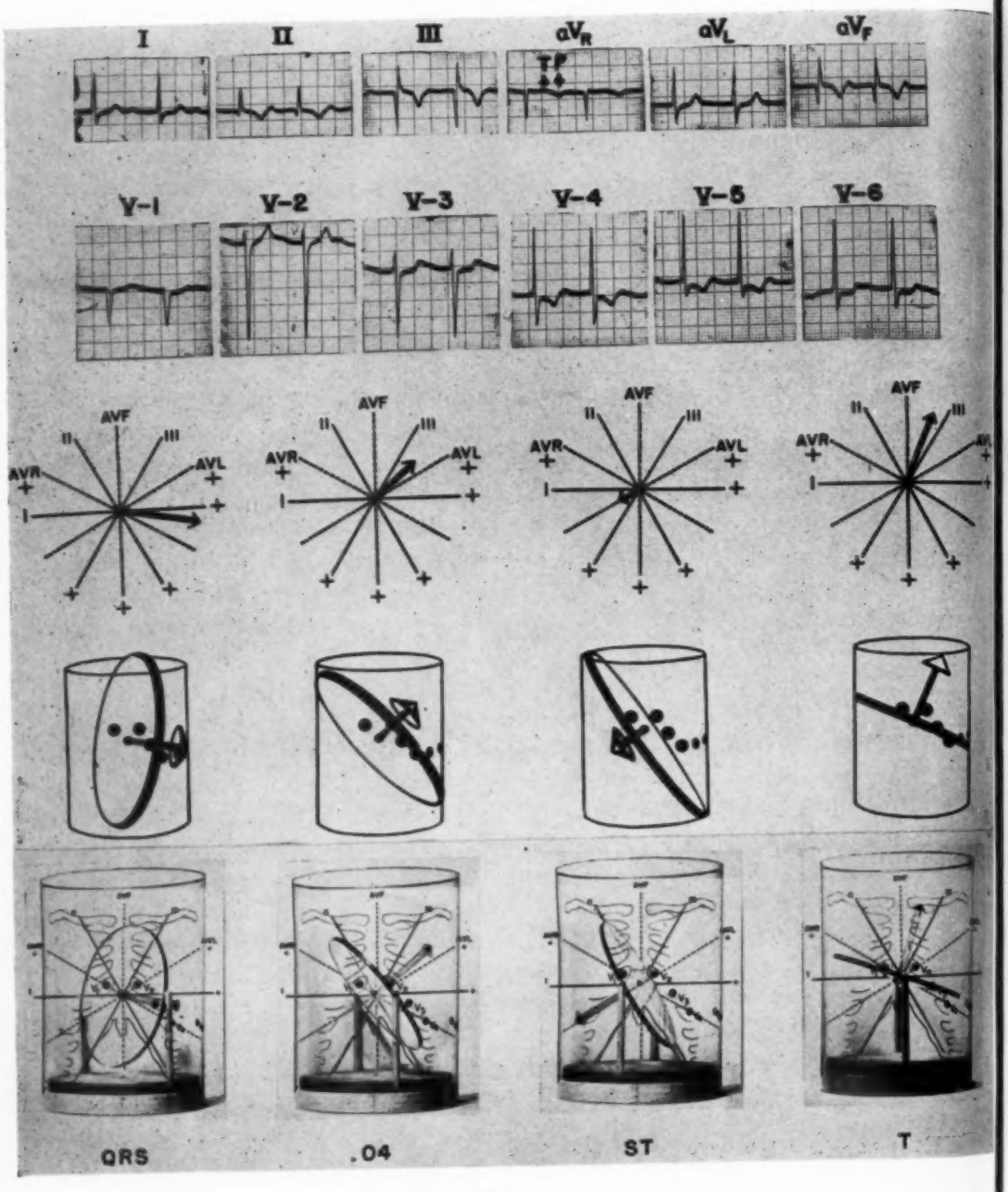

Fig. 3.

Fig. 4 illustrates a summary diagram showing the spatial electrical forces of a posterior myocardial infarction. Note that the arrow tips are tilted anteriorly or posteriorly so that their spatial orientation is similar to that defined by the isopotential plane. An illustration of this type can be used in reporting routine clinical electrocardiographic interpretations. The hexaxial reference system is conveniently printed on the electrocardiographic reporting forms by means of a rubber stamp.

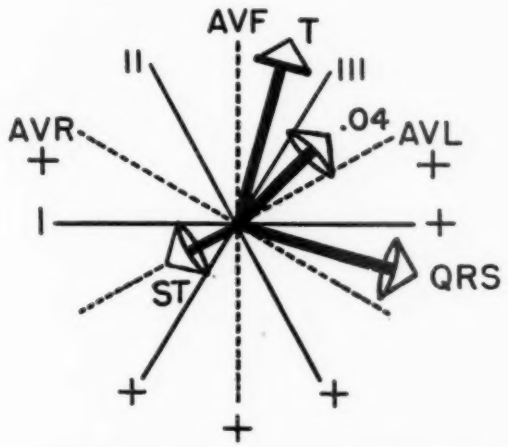

Fig. 4.—It is characteristic for the first 0.04 second of the QRS loop and the T vector to point away from an area of myocardial infarction while the mean S-T vector is directed toward the area of epicardial injury surrounding the infarction.

SUMMARY

1. A model useful in visualizing the spatial vectors of the heart is described.

2. Its usefulness is illustrated by a tracing of a posterior myocardial infarction.

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Clinical Reports

CONGENITAL CARDIAC ANOMALY: PERSISTENT COMMON ATRIOVENTRICULAR OSTIUM

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THE HEART described in this report is considered to be an example of persistent common atrioventricular ostium. In addition to the rarity of this cardiac anomaly, the case is of interest because the person was 58 years of age. Most persons with this lesion do not survive infancy.[1-13]

CASE REPORT

The patient was a 58-year-old white woman who was admitted to the hospital for the first time in 1944. Diagnosis then was a peranoid type of psychosis.

Physical Findings.—The blood pressure was 210/115 mm. Hg; a systolic murmur was heard at the aortic area; the lung fields were clear; there was edema of the legs, considered to be associated with varicose veins. An electrocardiogram showed left ventricular hypertrophy with depressed S-T segments.

Second admission was on Sept. 13, 1951. The history given by the patient's daughter was as follows: The patient had orthopnea and had not slept in a bed for more than one year. Six weeks previous to admission ankle edema was noted. Three weeks prior to admission jaundice developed; this was accompanied by chills, fever, dark urine, and clay-colored stools. The patient had been taking cation exchange resins for three weeks. Additional past history included a gall bladder attack eight years ago.

Physical Examination.—The patient was a well-developed, dyspneic, jaundiced white woman who was acutely ill. The conjunctivae were pale; the tongue was smooth and purple. Blood pressure was 110/75 mm. Hg. There was a harsh systolic murmur at the apex; the heart rhythm was regular, rate rapid; peripheral pulses were not obtainable. Râles were present in both bases of the lungs; the abdomen was distended; the liver was 6 cm. below the right costal margin and was tender; lower extremities showed massive edema. Fingers and toes were blue and cool.

Electrocardiography showed left bundle branch system block. There was Q_1 and QAV_L; there was possible lateral wall damage, first degree atrioventricular block, and auricular premature beats.

The patient expired twenty-four hours after admission.

Autopsy Report.—The body was that of an elderly white woman, said to be 58 years of age. The length of the body was 153 centimeters. The sclerae were icteric. The skin of the face and neck was bronze color. There was pitting edema of feet and ankles. The lungs showed moderate hyperemia and edema. There was moderate atherosclerosis of the branches of right and left pulmonary arteries. There were multiple thromboemboli in the smaller branches of pulmonary arteries. The heart was enlarged, weighing 450 grams.

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The liver was small, weighing 900 grams. On section, the central zones were prominent and the intrahepatic bile ducts were dilated. The gall bladder contained eighteen stones, of mixed cholesterol pigment type. There were yellow granules on the gall bladder mucosa, representing cholesterolosis. Cystic duct was patent. Common hepatic duct was dilated and the common bile duct was dilated to a circumference of 3 cm. There were six stones in the common duct. These were facetted, black in color, and firm.

The capsule of the spleen was slightly thickened; weighing 110 grams. Fifty cm. proximal to the ileocecal valve was a Meckel's diverticulum, 5 cm. in length, 3 cm. in diameter.

There was marked atherosclerosis of abdominal aorta with calcification and superficial ulceration. Ostia of the renal arteries were narrowed. The kidneys were reduced in size. The right kidney weighed 115 grams; the left kidney, 92 grams. There were stellate depressed scars on the surface of the kidneys. There were hemorrhages in the ovaries and endometrium.

Fig. 1.—Right auricle and ventricle showing the aperture, and the complete cleavage of the medial tricuspid leaflet:

1. The superior margin of the aperture is formed by the straight, free, inferior border of the interatrial septum; the triangular membranous tab is suspended from the anterior part of this border.

2. The walls of the aperture are formed by the anterior and posterior common leaflets, whose right halves represent the segments of the cleft medial tricuspid leaflet. These segments have a billowing character on this side.

3. The normal anterior and posterior tricuspid leaflets are continuous with the anamolous valve segments. The heart has been opened along the margo acutus.

4. The floor of the aperture is formed by the free superior border of the interventricular septum.

Description of the heart: The heart was enlarged. The superior vena cava was patent. Right auricular appendage contained an adherent thrombus, 1.2×0.3 cm. The interatrial septum was intact; its inferior edge was free, overhanging a defect in the atrioventricular and interventricular septa. The pars membranacea septi was completely missing (Fig. 1).

The free edge of the interatrial septum was 3.0 cm. below the limbus fossae ovalis and was continuous laterally with the attached margins of the posterior atrioventricular valve leaflets.

The free margin of the interatrial septum was 1.7 cm. in extent, was covered by a membranous ridge, and from its anterior 0.5 cm. was suspended a triangular membranous tab, 0.5 × 0.7 cm.

There was complete cleavage of the tricuspid and mitral valves, and these valves were continuous across the free concave superior border of the muscular interventricular septum (Fig. 2). Therefore, there was a single atrioventricular ostium guarded by a single valve of five leaflets. These were:

1. A normal anterior tricuspid leaflet, 2.5 cm. in width and connected by a chorda to a papillary muscle on the anterior wall of right ventricle.

2. A normal posterior tricuspid leaflet, 2.4 cm. in width, and connected by chordae to a papillary muscle on the posterior wall of right ventricle.

Fig. 2.—Left auricle and ventricle showing the aperture, the complete cleavage of the anterior mitral leaflet, and the absence of the valve commissure at the site of cleavage:

1. The anterior and posterior common leaflets pass through the aperture. The left halves of these leaflets represent the anterior and posterior segments of the cleft anterior mitral leaflet.

2. The normal posterior mitral leaflet is continuous with the anamolous valve segments.

3. There is a membranous band passing from the interatrial septum to the anterior common leaflet on this side. Just below this band the triangular membranous tab is attached.

3. An anterior common leaflet, 4 cm. in width, which crossed the septum and was common to both sides of the heart. The right side of this leaflet, for a width of 2 cm., had no free border, the inferior border was directly attached without chordae to the upper concave border of the interventricular septum. The superior end of this valve segment was attached directly to the aortic valve ring, and was continuous with the attached margin of the right aortic cusp (Fig. 3). This valve segment occupied the position of the caudal end of a normal conus septum. The valve tissue here was redundant and billowed into the right side of the heart. The left side of the anterior common leaflet was connected on its inferior end by chordae to a well-developed papillary muscle on the anterior wall of the left ventricle. The superior end of this valve segment was directly below the posterior aortic valve cusp. There was a membranous band 1.0 × 0.3 cm., extending from the left side of the interatrial septum to the auricular face of this valve segment. The membranous band began 2.0 cm. below the valvula foraminis ovalis.

4. A posterior common leaflet, 5.5 cm. in width, which crossed the septum and was common to both sides of the heart. At the point of crossing the septum, this leaflet was adherent for its

entire length of 1.6 cm. to the concave upper border of the interventricular septum. There was no communication between the ventricles below this leaflet. To the right of the septum, the valve tissue was redundant. The leaflet's free edge was connected by one chorda directly to the muscular septum and by three chordae to a small papillary muscle on the muscular septum. The left side of the posterior common leaflet was connected by chordae to a papillary muscle on the posterior wall of the left ventricle (Fig. 2).

5. A normal posterior mitral leaflet, 3 cm. in width, was connected by chordae to the posterior papillary muscle of left ventricle.

The aperture joining the left and right sides of the heart was semilunar in shape, measuring 3.2 cm. in anteroposterior dimension and 2 cm. in longitudinal dimension.

The cavum of right ventricle appeared slightly dilated. The wall of the right ventricle measured 0.8 cm. in thickness. Circumference of pulmonary valve was 7.8 cm. The wall of the left ventricle was 2 cm. in thickness. Aortic valve measured 7.2 cm., and there was distinct atherosclerosis of the coronary arteries with narrowing.

Fig. 3.—Left ventricle and aortic valve showing the anamolous valve leaflets in apposition:
1. The right half of the anterior common leaflet is attached below to the concave free border of the interventricular septum, and attached above to the aortic valve ring at the base of the right coronary cusp.
2. The left half of the anterior common leaflet is attached above to the aortic valve ring at the base of the posterior cusp.

DISCUSSION

The anomaly described was a result of two developmental failures. There was failure of: (1) fusion of dorsal and ventral endocardial cushions; and (2) complete caudad growth of septum aorto pulmonal.[14-18] Both of these events have normally occurred by the sixth week of embryonic life.

Endocardial cushions are formed by a proliferation of the lining membrane of the heart. These thickenings occur at the free margin of developing septa, and at the circumference of the common atrioventricular canal. The cushion tissue bordering the atrioventricular canal divides the canal into right and left ostia, forms the atrioventricular valve leaflets, and forms the pars membranacea septi.

The free edge of the septum aorto pulmonale fuses with the endocardial cushion plug which has divided the atrioventricular canal. Thereby, the interventricular septum is completed, and left ventricle blood is routed to the aorta and the right ventricle blood to the pulmonary artery. This fusion occurs at the right side of the endocardial cushion plug, that is, at the medial border of the right venous ostium.

Two of the findings in this heart are noteworthy. The first is the complete development of the interatrial septum. This accounts for the small size of the defect between the two sides of the heart. Other examples of persistent common atrioventricular canal have had an incompletely formed atrial septum and a consequent large aperture. The complete growth of septum primum and the formation of septum secundum are here demonstrably independent of fusion of the atrioventricular endocardial cushions.

Mall[15] writes: "The anterior endocardial cushion is a large sickle-shaped affair, and encircles the heart in front as the border of the atrial septum (septum primum) which is now forming. . . . The space in the atria between the cushions marks the primary foramen ovale I . . . ." and "Complete union of the two cushions has obliterated foramen ovale I." Tandler[18] writes: "Foramen ovale I closes by fusion of the free edge of septum primum with the endocardial cushsions of atrial canal." Two interpretations are possible: (1) endocardial tissue in the atria may fuse, completing the interatrial septum independent of fusion in the atrial canal, or (2) endocardial tissue in the atria is less important than Mall implies, and the primary septum atriorum is more important as Tandler states.

It has been recently suggested that persistent ostium primum is a less severe form of persistent common atrioventricular canal.[10] While these anomalies may occur together, one may be present to the exclusion of the other. In persistent ostium primum the atrioventricular valve rings are formed, the membranous septum is intact, and only the anterior mitral leaflet is cleft.[1,10,11,19-21] In examples of persistent common atrioventricular canal, the atrioventricular valve rings are incomplete, both tricuspid and mitral valves are completely cleft, the membranous septum is missing, and the interatrial septum is either intact or defective to a varying degree.

The second noteworthy finding is the membranous band extending from the interatrial septum to the auricular face of the anterior common leaflet. Examples of persistent ostium primum have a cleft anterior mitral leaflet. Tandler[18] writes that the septum atriorum is attached to the endocardial cushions farther to the left than the attachment of the interventricular septum. These observations suggest that the central portion of the anterior mitral leaflet is formed from either (1) the atrial extensions of the endocardial cushions which in fusion reach the level of the canal, or (2) endocardial tissue on the free edge of septum primum.

The functional defect in this heart has apparently been reduced by the position of the right side of the anterior common leaflet. This valve segment effectively covers the anterior one-half of the aperture. The position and attachments of the valve tissue suggests that it was functioning as a septum. Odgers[16] and Kramer[14] write that the conus ridges fuse with the right tubercles of the anterior and posterior endocardial cushions. The impression is that the right side of the anterior cushion has extended toward the incompletely formed conus septum.

SUMMARY

An example is presented of persistent common atrioventricular ostium in a 58-year-old woman. The defect is considered to be a failure of fusion of the endocardial cushions. The special configuration of the defect, and the arrangement of the anomalous valve is considered to be a failure of the septum aorto pulmonale to form completely.

The well-developed interatrial septum is offered as evidence that atrial septum development is independent of the endocardial cushions at the canal level.

Mention is made of a cleft anterior mitral leaflet in examples of persistent ostium primum. Distinct redundant membranous tissue on the free edge of the atrial septum suggests that a normal anterior mitral leaflet is completed by tissue from the atria.

The functional defect was probably reduced by the attachment of the anomalous valve segments to the borders of the septal defect.

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PAROXYSMAL AURICULAR TACHYCARDIA WITH DIGITALIS-INDUCED ATRIOVENTRICULAR BLOCK UNDER OBSERVATION FOR THIRTEEN YEARS

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THE PATIENT, in this report, has been observed since the age of 32 and is at present 45 years old. During the past eleven years he has experienced innumerable paroxysms of auricular tachycardia lasting from several minutes up to 498 days. Fortunately digitalis was effective in producing an atrioventricular block with slowing of the ventricular rate, so that his congestive failure was controlled and he was able to carry on his regular activities during most of this time.

CASE REPORT

L. K., a 45-year-old man, was first seen on Jan. 11, 1939, after having been rejected for life insurance. He had no complaints and felt well. The findings on physical examination were essentially normal except for the presence of frequent premature contractions. The heart appeared normal on auscultation, and on fluoroscopy showed no enlargement. Blood pressure was registered at 110 mm. Hg systolic and 80 mm. Hg diastolic. The electrocardiogram (Fig. 1,*A*) revealed normal sinus rhythm with very low P waves in Leads I and III, and broad low bifid P waves in Lead II. Occasional auricular and ventricular premature beats were present.

The patient remained symptomless until 1941, when he experienced three short attacks of severe palpitation with rapid regular heart action. On Oct. 20, 1941, he was seen in the office during such an attack. The heart rate was found to be regular and rapid at 220 per minute. The electrocardiogram (Fig. 1,*B*) disclosed a supraventricular tachycardia. Carotid sinus stimulation, eyeball pressure, and then 25 mg. of Mecholyl Chloride, administered subcutaneously, had but a slight transient effect on reducing the rate. The patient was then admitted to the Jewish Hospital, Brooklyn. In the hospital, 8 c.c. of Cedilanid, given intravenously, produced a 2:1 and 3:1 atrioventricular block with a fall in the ventricular rate to 100; the auricular tachycardia remained unaltered. However, after three days without any subsequent administration of digitalis, the atrioventricular block disappeared and the rapid ventricular rate returned. Quinidine sulfate in increasing doses up to 0.6 Gm. every two hours resulted only in slowing of the heart rate to 145 with widening of the QRS complexes to 0.13 second. Quinine dihydrochloride, 1 Gm. given slowly intravenously, then slowed the rate to 140. The administration of Prostigmine, ipecac with the resultant vomiting, and a repetition of the Mecholyl Chloride resulted merely in a momentary slowing of the tachycardia. On his sixth day at the hospital, while the ventricular rate was 190, congestive heart failure became apparent with distension of the neck veins, basal pulmonary râles, and enlargement of the liver to the umbilicus. He was then given a mercurial injection and redigitalized rapidly. On the next day congestive failure had diminished considerably, and the ventricular rate had fallen to 100 with 2:1 atrioventricular block. On the fourteenth hospital day while on a maintenance dose of digitalis, the auricular tachycardia subsided spontaneously, the electrocardiogram then revealing normal sinus rhythm with a heart rate of 80.

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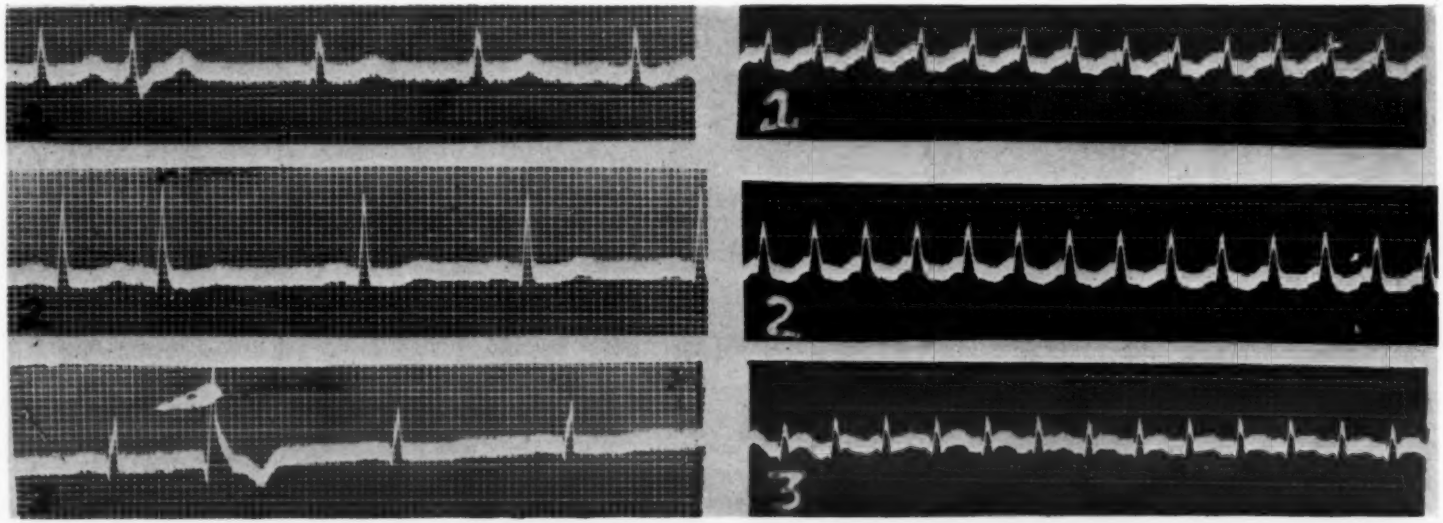

A. *B.*

Fig. 1.—*A*, (Jan. 11, 1939.) Normal sinus rhythm. P waves are poorly seen in Leads I and III. In Lead II, low bifid P waves are evident. Auricular and ventricular premature beats are present. Standardization, 1 millivolt = 10 mm.

B, (Oct. 20, 1941.) Auricular paroxysmal tachycardia at a rate of 220. Standardization, 1 millivolt = 10 mm.

The basal metabolism was reported at −8 per cent, and the roentgenogram of the chest exhibited a heart of normal size. Patient was discharged feeling well although still weak.

The patient felt well for the next sixteen months until March 5, 1943, when he experienced another attack of tachycardia lasting twenty-four hours. Two other seizures, persisting seventeen days and thirteen days, occurred in 1943. Digitalis again produced atrioventricular block with subsequent slowing of the ventricular rate to 90:125. Quinidine had no effect either in preventing or shortening these attacks. Fig. 2, an electrocardiogram taken during one attack, shows a predominant 2:1 atrioventricular block with a ventricular rate of 124. With eyeball pressure, the block was temporarily increased so that P′ waves, the bifid auricular waves of the tachycardia, were clearly visible and were quite similar to the patient's normal P waves.

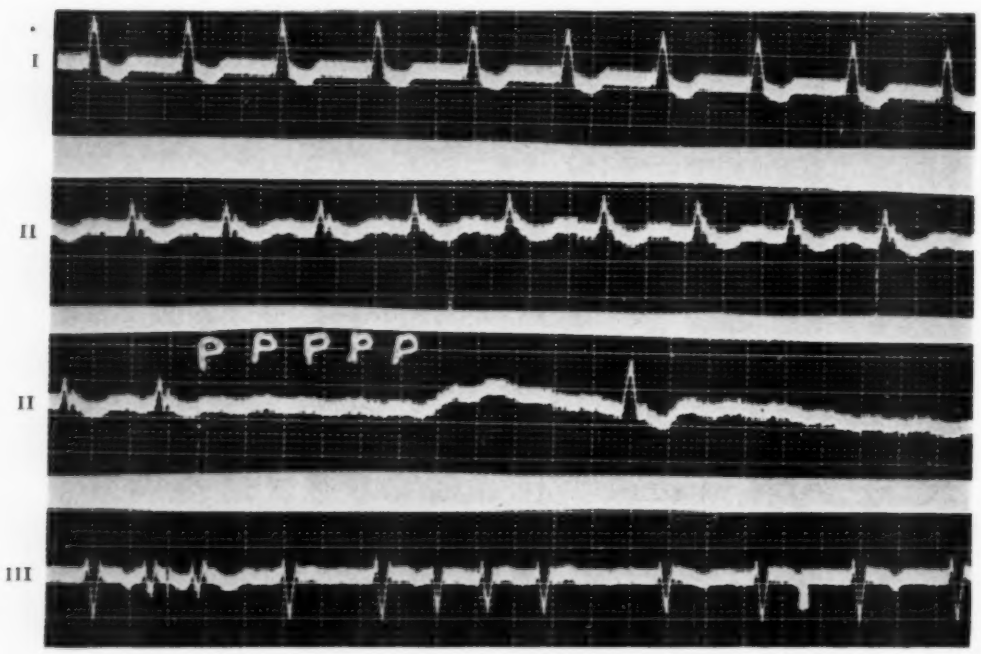

Fig. 2.—(Dec. 22, 1943.) In Leads I and II, 2:1 auricular tachycardia is present with a ventricular rate of 124. In Lead II, only alternate auricular waves with a P-R interval of 0.24 second are seen, the others being masked by the ventricular complexes. In the next Lead II, pressure on the eyeballs has produced a marked atrioventricular block, up to 10:1, demonstrating the underlying auricular tachycardia at a rate of 248. In Lead III, irregular ventricular responses, some at 1:1, are evident. Standardization, 1 millivolt = 10 mm.

From 1944 until the present time, the patient has been kept continuously on maintenance doses of digitoxin, 0.2 mg. about four times a week. This was done in order to slow the ventricular rate whenever an attack of paroxysmal auricular tachycardia might occur. In 1944 one attack lasted for fifteen days and many other shorter episodes were experienced. In 1945 several short paroxysms occurred, and then there were five longer seizures of 15 days, 10 days, 110 days, 10 days, and 10 days. In Fig. 3, the electrocardiogram shows a varying atrioventricular block with a constant auricular tachycardia at a rate of 224. In order to increase the auricular deflections, the electrocardiograph was standardized so that 1 millivolt produced a deflection of 20 mm. In 1946 three attacks of one-half hour's, five days', and nine days' duration occurred.

In 1947 the patient complained of many short nocturnal seizures, and for the first time experienced precordial and substernal pressure pain on walking, which was relieved by rest. An episode of auricular tachycardia started on Nov. 15, 1947, and persisted until April 2, 1949, a total of

498 days. During this time, digitalis was administered in maintenance doses and the resultant atrioventricular block kept the ventricular rate down to 80:110. When the patient stopped the drug, the rate rose and when too much of the drug was taken, the patient complained of blurred and colored vision. At times, the persistence of the auricular tachycardia could be diagnosed by a doubling of the cardiac rate when the patient exercised. At other times, an electrocardiogram (Fig. 4) was necessary in order to determine whether or not the abnormal auricular tachycardia was still present.

In 1950 there was an attack of fifty-five days' duration. Oral Pronestyl Hydrochloride was administered without effect. In 1951 several short paroxysms were experienced as well as one of thirteen days' duration. During 1952 he has suffered only short attacks.

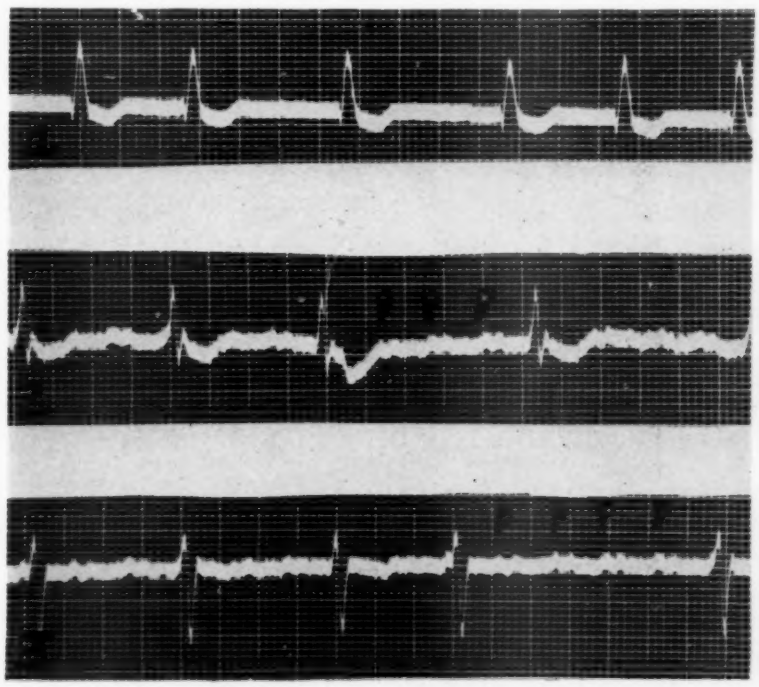

Fig. 3.—(Aug. 10, 1945.) Varying atrioventricular block with auricular tachycardia. Bifurcated auricular waves are well seen in Leads II and III at a rate of 224 per minute. The ventricular response is irregular with R-R intervals occurring in multiples of 2:1 to 5:1. Standardization, 1 millivolt = 20 mm. This has been done in order to increase the deflections of the auricular waves.

During these years, the heart has shown progressive deterioration and its transverse diameter has gradually increased until the left ventricle has now become markedly enlarged. Congestive heart failure has become more evident with prominence of the neck veins, occasional basal râles, enlargement of the liver, and moderate leg edema. The patient now requires a low-sodium diet and an occasional mercurial injection. He suffers from angina of effort and finds it necessary to walk slower than before. Nevertheless, he is ambulatory and maintains his regular working hours. A recent electrocardiogram (Fig. 5) shows normal sinus rhythm. The previous bifid P waves are no longer seen in the limb leads, and only those recorded from the third and fourth intercostal spaces to the right of the sternum reveal auricular waves. These waves have been brought out by increasing the deflections of the string by standardizing so that 1 millivolt produced a deflection of 20 mm. The QRS complexes, accordingly, are of low voltage in the limb leads and are also widened to 0.12 second.

DISCUSSION

The subject of this report probably always had an abnormality of auricular excitation. This view is supported by the presence of abnormal P waves in the record taken before the onset of the paroxysms of auricular tachycardia. In 1939, the P waves were almost absent in Leads I and III and were low and bifurcated in Lead II. After four years of paroxysms of tachycardia, the normal sinus P waves could no longer be identified in the limb leads and could be seen only in special auricular leads taken from the upper right sternal border. Before the onset of the tachycardia, the patient also manifested increased myocardial irritability as shown by the presence of frequent auricular and ventricular premature contractions.

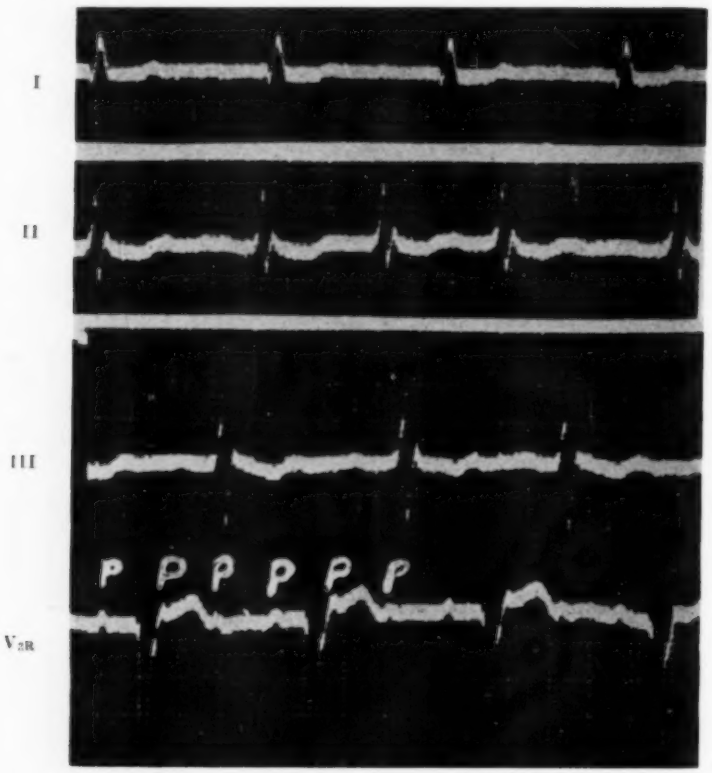

Fig. 4.—(March 6, 1948.) Predominant 3:1 response to the auricular tachycardia. The regularity in Leads I and III might suggest normal sinus or nodal rhythm; however, Lead V_{3R} shows a definite auricular tachycardia at a rate of 216. The ventricular rate is 72, except in Lead II where there are some 2:1 ventricular responses. Standardization, 1 millivolt = 20 cm.

It is interesting to observe that the auricular waves registered during the tachycardia were bifid and similar to the auricular waves obtained during normal sinus rhythm. This suggests that the abnormal auricular focus was probably located constantly near the sinoauricular node. This observation has also been noted by Barker and associates[1] and Alimurung and associates.[2] Barker and associates used esophageal and supra- to infrasternal leads to pick up the auricular waves during the tachycardia.

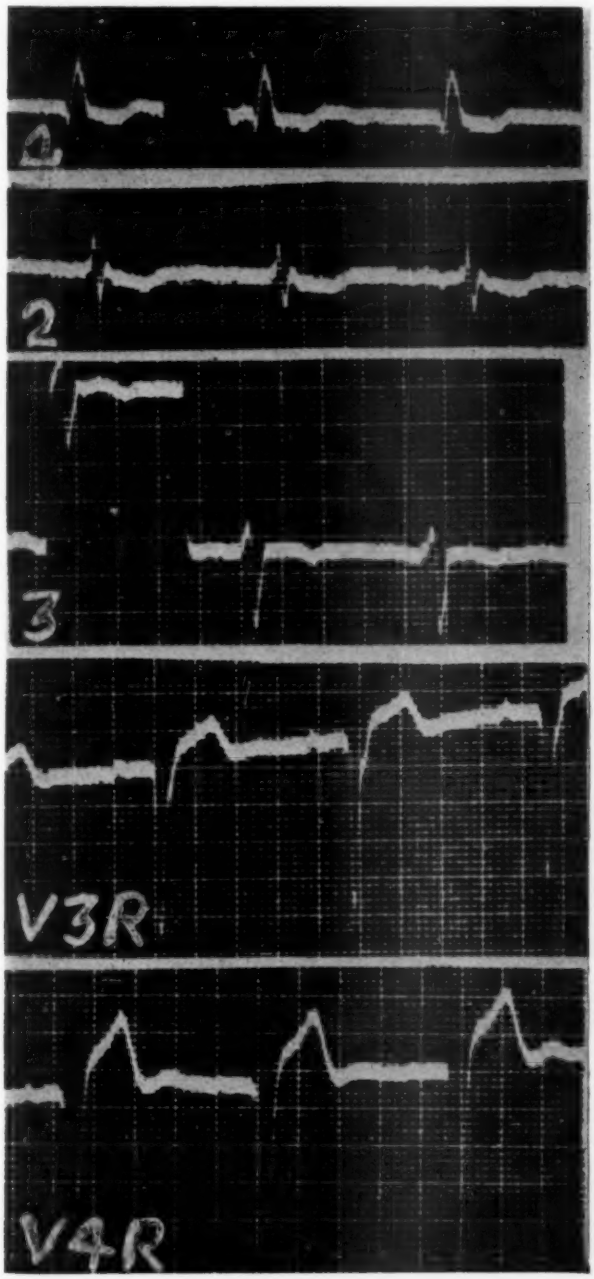

Fig. 5.—(May 6, 1950.) Normal sinus rhythm. P waves can be seen only in V_{3R} and V_{4R}, and the P-R interval is 0.2 second. QRS complexes are of low voltage and are widened to 0.12 second. T waves show a digitalis effect. Standardization, 1 millivolt = 20 mm.

The differentiation of auricular tachycardia from auricular flutter rests mainly on the demonstration of an isoelectric period at some time during the P-P interval not only in any one lead but in all recorded leads. If a sine wave or sloping line is registered in any lead, flutter should be diagnosed. The rate in the latter is usually over 250 while the rate in the auricular tachycardia is ordinarily slower than this. Many cases of paroxysmal auricular tachycardia with atrioventricular block, reported in the literature, have shown prior or subsequent change to auricular flutter or fibrillation. This alteration has not been demonstrated in the present reported case.

The patient's heart has shown evidence of deterioration during the years of paroxysmal auricular tachycardia even though the ventricular rate has been kept below 100 most of the time. The heart, originally of normal size, has progressively increased until the left ventricle is now markedly enlarged. There has been a slow gradual advance in congestive failure and angina pectoris. Successive electrocardiograms have demonstrated the appearance of intraventricular block and low voltage of the QRS complexes in the limb leads.

Digitalis has been the only successful drug in the treatment of this patient. It has kept the ventricular rate at a tolerable level so that congestive failure was controlled, and he has been able to continue at work. All other drugs, quinidine, quinine, Mecholyl Chloride, Prostigmin, methlsulfate, Pronestyl Hydrochloride and ipecac were without any beneficial effect, and mechanical procedures such as carotid sinus stimulation and eyeball pressure were but of momentary influence.

SUMMARY

A case with innumerable paroxysms of auricular tachycardia during the past eleven years is reported. The attacks have lasted from several minutes up to 498 days. Digitalis, by producing atrioventricular block and slowing the ventricular rate, was found to be the only drug of therapeutic value.

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A CASE OF WOLFF-PARKINSON-WHITE SYNDROME WITH PAROXYSMAL VENTRICULAR TACHYCARDIA

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THE PAROXYSMAL tachycardia commonly associated with the Wolff-Parkinson-White syndrome,[1] is of the auricular type. Ventricular tachycardia may occur, but is rare. A search of the literature has revealed only seven references to the latter variety.[2-8] It is for this reason that the following case is reported.

CASE REPORT

At 11:00 P.M. on Nov. 16, 1950, a 25-year-old married woman had a sudden attack of violent palpitations associated with giddiness and weakness, and a choking sensation in the throat. This was soon followed by a feeling of pressure behind the sternum, radiating to both arms. At midnight the patient was seen by her doctor who found her collapsed with profuse sweating, vomiting, and an ashen color. Her radial pulse was irregular and varied in rate from 10 to 50 per minute. When examined one hour later, the heart sounds were extremely rapid and distant, resembling the ticking of a small watch, but with sounds of normal intensity irregularly interspersed. Signs of congestive failure were not in evidence. An electrocardiogram revealed ventricular tachycardia at the rate of 300 beats per minute (Fig. 1). One relatively normal complex was to be seen in Lead I. Its S-T segment was noticeably depressed, whereas a similar complex in Lead III displayed S-T elevation. The immediate clinical impression was that the patient was suffering from myocardial infarction with paroxysmal ventricular tachycardia. Eyeball and carotid sinus pressure did not affect her condition. Morphine, ¼ grain, was administered subcutaneously as well as quinidine sulfate, 12 grains, by mouth. The quinidine was repeated in 5-grain doses every two hours. By 7:30 A.M. on Nov. 17, 1950, the patient's condition had improved slightly, and an electrocardiogram showed paroxysmal ventricular tachycardia as before, with runs of atrioventricular nodal tachycardia (Fig. 2). Sudden reversion to normal rhythm occurred soon afterwards, that is, nine hours after the onset of the attack. The electrocardiogram then showed the appearances typical of the Wolff-Parkinson-White syndrome[1] (Fig. 3).

The patient remained quite well, and no abnormality was noted on physical examination when she was next seen one month later. The fluoroscopic appearances of the chest were normal but the electrocardiogram again showed shortened P-R intervals and broadened QRS complexes. The ballistocardiogram done with the portable instrument of Dock and Taubman[10] was normal (Fig. 4).

A second attack occurred at 10:00 A.M. on Sept. 9, 1951. It consisted of palpitations, vomiting, and sweating, but was not accompanied by pain. Five-grain doses of quinidine were prescribed every hour. An electrocardiogram taken five hours after the onset of the symptoms again revealed paroxysmal ventricular tachycardia (Fig. 5). One Gm. of Pronestyl Hydrochloride (procaine amide hydrochloride, E. R. Squibb & Sons) was given by mouth, followed by a further 250 mg. one hour later. The rhythm reverted to normal at 5:20.P.M, and the tracing once again showed the appearance typical of the Wolff-Parkinson-White syndrome. The patient has remained well since then. A further electrocardiogram taken on Nov. 22, 1951, was identical to the one shown in Fig. 3.

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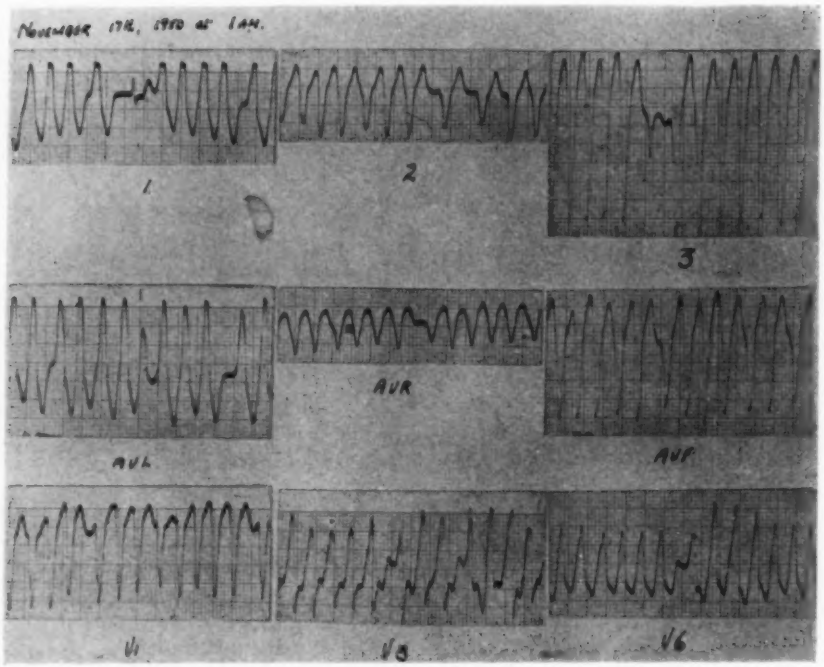

Fig. 1.—Electrocardiogram showing ventricular tachycardia. Note the S-T depression in one complex of Lead I, and the S-T elevation in one complex of Lead III.

Fig. 2.—Lead aV_L showing the change from ventricular to nodal tachycardia.

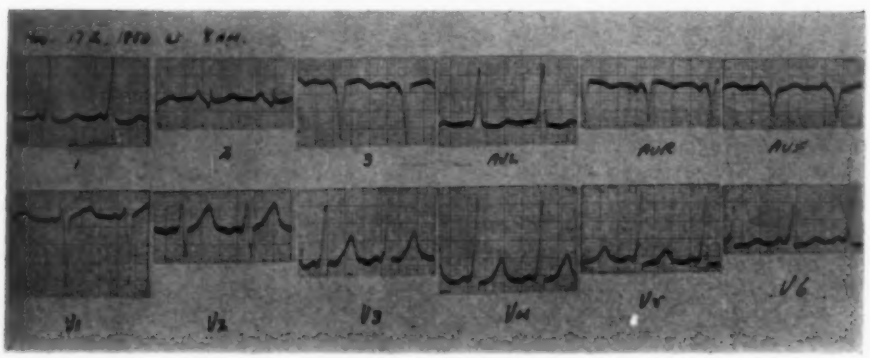

Fig. 3.—Electrocardiogram taken at the termination of the attack of ventricular tachycardia revealing short P-R intervals and broadened QRS complexes typical of the Wolff-Parkinson-White syndrome.

DISCUSSION

Littman and Tarnower[6] include in their series of nine cases of Wolff-Parkinson-White syndrome two cases with tracings resembling those of this case. They consider them to be examples of auricular fibrillation with prolonged and dis-

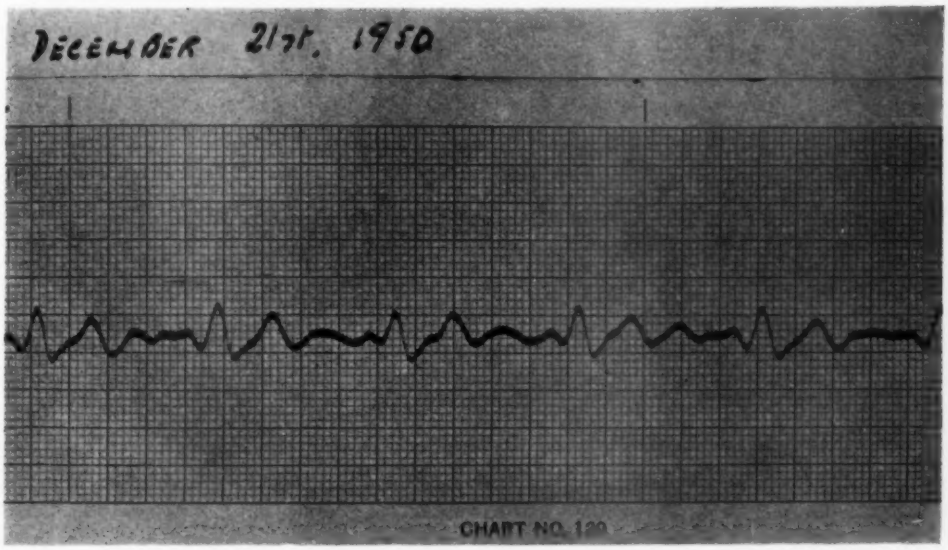

Fig. 4.—A normal ballistocardiogram taken one month after the attack of tachycardia.

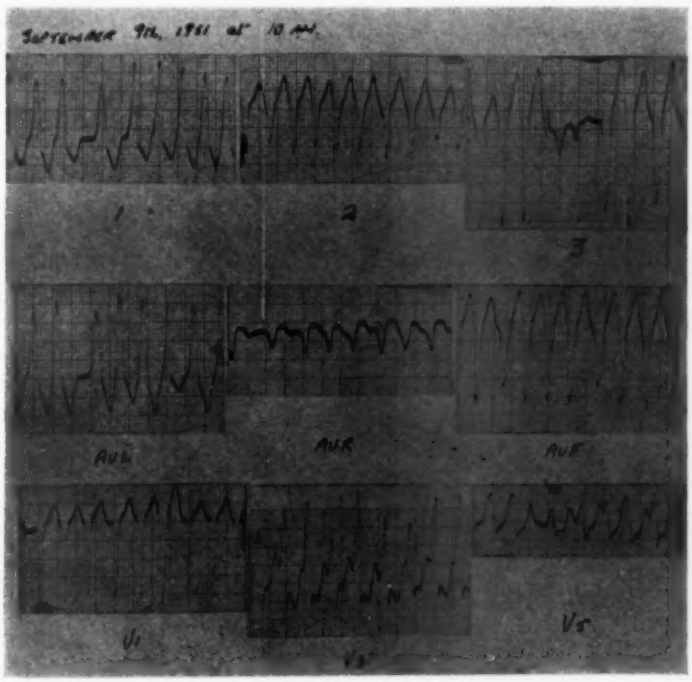

Fig. 5.—An electrocardiogram illustrating the second attack of paroxysmal ventricular tachycardia.

torted QRS complexes. Similar tracings reproduced in the other papers referred to above are regarded as examples of ventricular tachycardia. Fox and associates[9] have recently made some interesting suggestions in regard to the mechanism of ventricular tachycardia in cases of Wolff-Parkinson-White syndrome. They state that it is ". . . the result of a combination of aberrant pathway block and the increase in the influence of cholinergic substances on the A-V node." Palatucci and Knighton[5] were able to demonstrate changes in the T waves of their cases of Wolff-Parkinson-White syndrome by the use of atropine. No attempt was made to observe these effects in this case. Clearly the depressed S-T segment to be seen in one complex of Lead I of the original electrocardiogram and the elevated S-T segment in one complex of Lead III (Fig. 1) were the result of profound myocardial ischemia resulting from the tachycardia.

My thanks are due to Dr. I. Sherr for allowing me to record this case.

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BILATERAL PHEOCHROMOCYTOMA ASSOCIATED WITH NEUROFIBROMATOSIS

Death Following Aortography

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PHEOCHROMOCYTOMA and neurofibromatosis appear to occur together oftener than chance should occasion. Of 203 cases of pheochromocytoma collected from the literature in 1950, Davis and associates[1] found that ten also had neurofibromatosis. Various measures employed for the localization of pheochromocytomas prior to operation include massage in the adrenal areas, intravenous pyelography, retroperitoneal pneumography, and laminagraphy. Smith and associates[2] have reported translumbar arteriography to be a diagnostic procedure of value in a variety of intra-abdominal and retroperitoneal conditions. In their hands this procedure has not been associated with any serious reactions in over 1,000 cases, and they suggested that it might be of value in localizing adrenal tumors. Nelson[3] has used this method on several occasions in patients with pheochromocytomas. It is the purpose of this paper to report a fatal reaction following the successful aortographic visualization of a pheochromocytoma in a patient with neurofibromatosis.

CASE REPORT

A 50-year-old white man, a retired soldier, entered the hospital on Dec. 28, 1951 complaining of tarry stools. He estimated that he had passed approximately one quart of dark tar-like material with no associated hematemesis, pain, or weakness. There was a history of similar symptoms in July, 1945, for which he had been given four transfusions of whole blood. At that time a roentgenographic study of the gastrointestinal tract established the presence of a duodenal ulcer and led to his retirement from the Army in February, 1946. He had had two subsequent episodes of melena, one in June, 1946, and one in the spring of 1951; both had been mild and responded readily to treatment. There had been no other associated gastrointestinal symptoms.

Three or four years before admission, the patient had first become aware of numerous soft tumors beneath the skin. These were asymptomatic, but a biopsy of one of them had been performed and a diagnosis of neurofibroma established. The family history revealed that the patient's mother, a diabetic, had died at the age of 45 years from carcinoma of the breast. An aunt and an uncle had also died of carcinoma.

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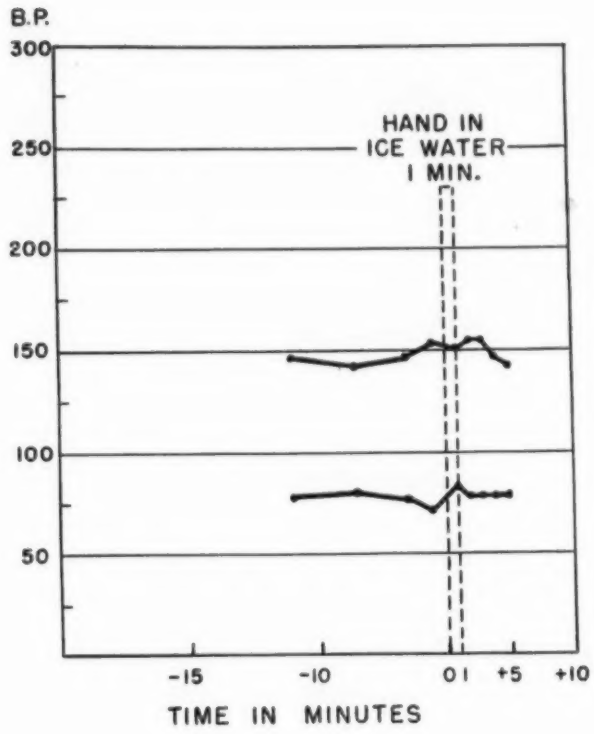

Fig. 1.

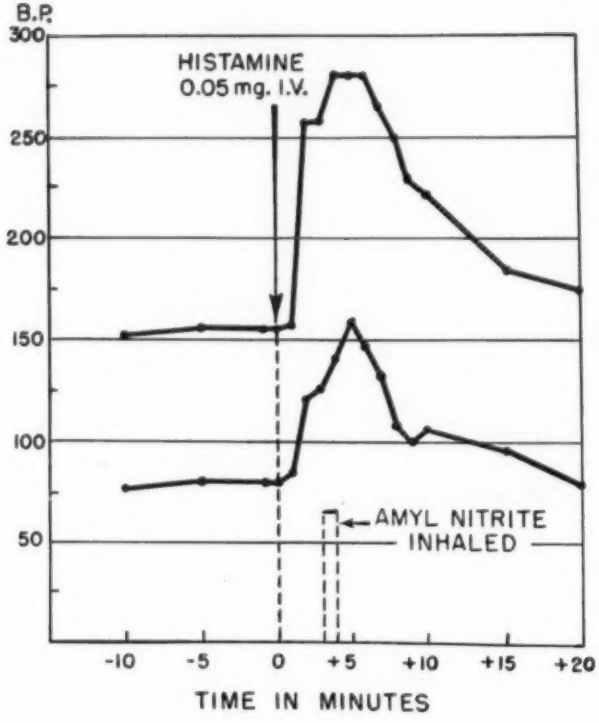

Fig. 2.

Fig. 1.—Cold pressor test illustrating blood pressure response after immersion of one hand in ice water for one minute.

Fig. 2.—Blood pressure response following injection of 0.05 mg. of histamine intravenously.

Physical examination revealed a well-developed, moderately obese white man, 64 inches in height, and weighing 180 pounds, who did not appear acutely ill. There were numerous soft cutaneous tumors scattered diffusely over the entire body surface; some were pedunculated, and they ranged in size from 0.5 to 2.0 cm. in diameter. Several *cafe au lait* spots were present. The ocular fundi were normal. Examination of the heart and lungs was normal. The pulse was regular at a rate of 100 per minute, and the initial blood pressure was 210/110 mm. Hg. There was moderate tenderness to palpation in the right upper quadrant of the abdomen, but no masses were palpable.

During the performance of a gastric analysis following the injection of histamine, the patient developed dyspnea, palpitation, diaphoresis, and a generalized pounding headache. Further questioning then revealed that for four or five years he had had recurrent periods of similar symptoms except that previously no headaches had been present. These episodes had not been as severe as the one following histamine injection, and had occurred at irregular intervals, seemingly related to long periods of bending and lifting. These attacks had lasted from a few minutes to as long as one hour, during which he had perspired more profusely than was usual for him.

Laboratory studies revealed a leukocyte count of 17,600 per cumm. with a normal differential cell count. The hemoglobin was 14 grams per 100 c.c. Corrected erythrocyte sedimentation rate (Wintrobe) was 20 mm. per hour. A persistent leukocytosis was present during hospitalization, and on the day before death the leukocyte count was 23,900. Urinalysis at the time of admission showed a 2 plus reaction for albumin. Subsequent urinalyses showed no albumin, but glycosuria ranging from a trace to 2 plus was observed. Phenolsulfonphthalein excretion was 66 per cent in two hours. A urinary concentration test showed a maximum specific gravity of 1.025. Urea clearance tests performed on two occasions revealed values of 71 and 74 per cent of average normal function. Nonprotein nitrogen was 37 mg. per cent. Serum cholesterol was 218 mg. per cent and cholesterol esters were 164 mg. per cent. Stool examinations for occult blood (guaiac) were strongly positive on admission. Fasting blood sugars on two occasions were 155 and 177 mg. per cent. A glucose tolerance test revealed the following findings: fasting blood sugar 145 mg. per cent; one hour, 221 mg. per cent; two hours, 171 mg. per cent; three hours, 111 mg. per cent. Glycosuria was present in urine samples taken one, two, and three hours after oral administration of glucose. Roentgenograms of the chest and skull were normal. A roentgen study of the upper gastrointestinal tract showed deformity of the duodenum with an ulcer crater near the base of the bulb. The electrocardiogram showed no abnormality except for prolongation of the corrected Q-T interval to 0.43 second.

After admission of the patient to the hospital, he had no further bleeding from the gastrointestinal tract. Following one week of treatment consisting of bed rest, a Sippy diet, and the administration of antacids, the stools were of normal color and the test for occult blood was only faintly positive. When histamine injection, during the course of a gastric analysis, was followed by a marked elevation of blood pressure, the possibility of pheochromocytoma was suspected. Since the patient's blood pressure averaged about 150/90 mm. Hg, the cold pressor, histamine, and Mecholyl Chloride provocative tests were performed. (Figs. 1, 2, and 3.) Benzodioxane was injected intravenously with the intention of blocking the pressor response to histamine, which was injected six minutes later (Fig. 4).

The results of these tests were considered to be positive, indicating the presence of pheochromocytoma. Attempts were then made to localize the tumor. Intravenous pyelograms showed no abnormality in the position of either kidney. Two attempts to introduce oxygen retroperitoneally for pneumography were unsuccessful, and massage in the adrenal regions produced no clear-cut response. It was, therefore, decided to attempt localization of the tumor by means of serial roentgenograms taken after injection of contrast material (iodopyracet) into the abdominal aorta through a translumbar approach. This procedure was performed under intravenous Pentothal Sodium anesthesia on Feb. 8, 1952, and revealed a large tumor in the right adrenal area in which many dilated blood vessels were present (Fig. 5).

After the patient was returned to bed, his blood pressure was found to be 270/130 mm. Hg. It gradually fell to an average level of 160/100 mm. Hg during the ensuing six hours. About ten hours following arteriogram the patient became mentally disoriented. A short time later he attempted to get out of bed and fainted. At this time the extremities were cold and clammy and

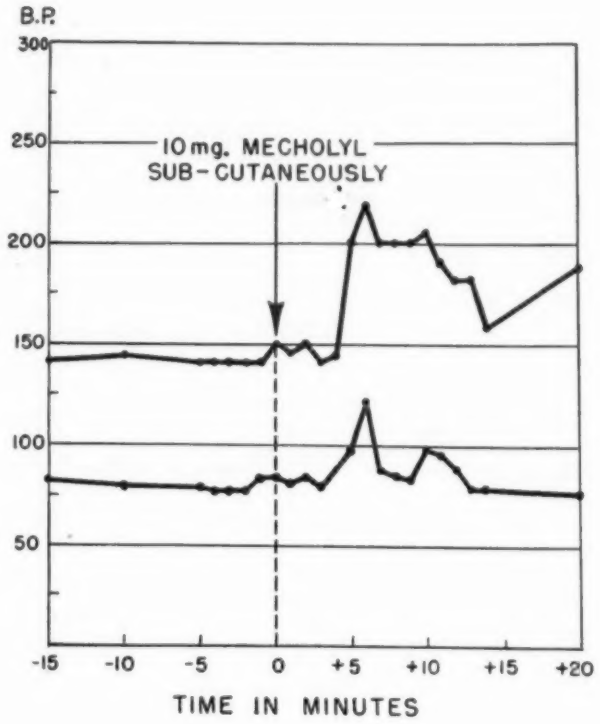

Fig. 3.

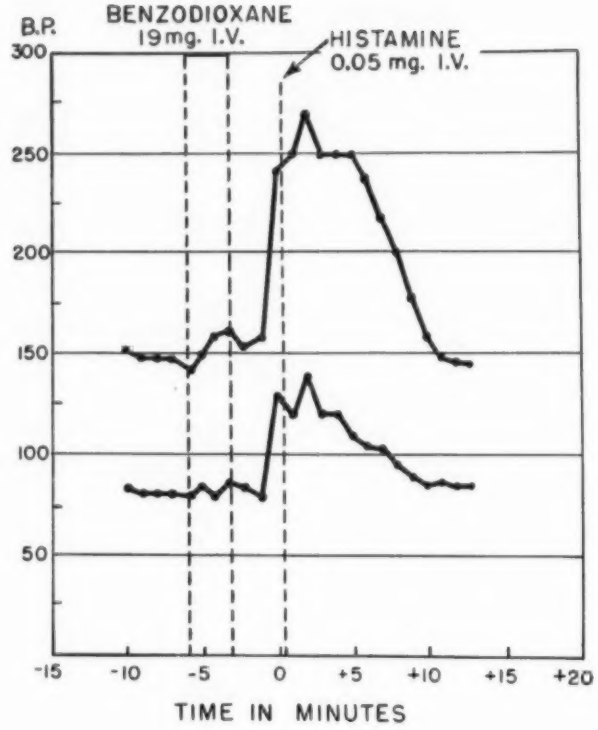

Fig. 4.

Fig. 3.—Blood pressure response following injection of 10 mg. of Mecholyl Chloride subcutaneously.

Fig. 4.—Paradoxical rise of blood pressure after injection of 19 mg. of benzodioxane intravenously. Injection of 0.05 mg. of histamine intravenously six minutes later caused only a slight additional increase in blood pressure level.

the lips and nails were cyanotic. Blood pressure was 170/110 mm. Hg, but because the patient appeared to be in shock clinically, he was placed in Trendelenburg position and oxygen was administered. The blood pressure then fluctuated between 145/96 and 196/145 mm. Hg until approximately twelve hours after the arteriogram when it suddenly fell to 98/80 mm. Hg. The administration of physiologic saline solution followed by plasma and whole blood intravenously succeeded in maintaining the blood pressure at relatively normal levels. The patient, however, continued to be cyanotic and the extremities were cold and clammy. The pulse was rapid and at times not palpable. Six hours later abdominal distention developed and was accompanied by the passage of a liquid bloody stool. Shortly thereafter no peristaltic sounds were heard and continuous aspiration of gastric contents with a Miller-Abbott tube was instituted. Supportive treatment was continued with intravenous infusion of whole blood, but the blood pressure could not be maintained, and the pulse continued to be rapid, weak, and thready. The patient expired approximately thirty-six hours after the arteriogram was performed.

Fig. 5.—Roentgenogram of right adrenal tumor taken following the injection of iodopyracet into the aorta through a translumbar approach. (From Letterman Army Hospital Medical Illustration Section. Neg. No. L6733-7.)

Necropsy performed ten hours after death revealed many small, soft cutaneous nodules of various sizes scattered over the extremities and torso. Two small scars were noted in the first part of the duodenum. In the jejunum there was an irregular, firm, intraluminal sessile tumor which projected 4 cm. above the serosa and contained some central ulceration. Several similar smaller nodules were present in the jejunum. There was a retroperitoneal hemorrhage about the posterior wall of the abdominal aorta at the level of the superior mesenteric artery measuring $5 \times 4 \times 1$ cm. in size. No gross evidence of thromboses in any of the abdominal arteries was noted.

Microscopic study of the spleen and several mesenteric lymph nodes revealed an infiltration of neutrophils and eosinophils. Histologically the skin tumors were neurofibromas and the jujunal tumor was a leiomyoma. The liver showed a marked fatty replacement with minimal portal fibrosis. Many of the smaller arterioles of the spleen, pancreas, and kidneys showed a moderate to marked subendothelial hyalinization, causing narrowing of some of their lumina. In the kidneys some glomeruli contained small eosinophilic hyaline thrombi which had occluded some of the capillaries. Many of the convoluted and collecting tubules showed a marked cellular cloudy swelling and hydropic degeneration with a decrease in the number of nuclei. A few convoluted tubules and many of the collecting tubules contained pale eosinophilic hyaline casts. In the pituitary there was a marked increase in beta cells, and material which stained with periodic acid was noted both within and between some of them. A small adenoma was present in the thyroid gland.

The left adrenal gland weighed 11 grams and the medulla contained a round nodule, 1 cm. in diameter, which was dull orange-tan, homogeneous, and poorly circumscribed. The remainder of this adrenal was essentially normal on gross examination. In the region of the right adrenal gland there was a 12 × 9 × 3.5 cm. tumor which weighed 380 grams (Fig. 6). At the superior pole of this tumor remnants of adrenal tissue were found compressed and flattened. The tumor was located just to the right side of the inferior vena cava, was intimately adherent to it, and displaced it toward the left. The tumor was closely adherent to the liver posteriorly and superiorly and to the right kidney inferiorly. It was oval, slightly irregular, somewhat lobulated, and had a capsule which averaged about 2 mm. in thickness. Some areas of the tumor were firm and other areas were soft and fluctuant. The cut surface of the tumor was succulent with moderate bulging. It contained many irregular, dull yellow-orange nodules which were interspersed by areas of necrosis and hemorrhage. Narrow cream-colored fibrous bands divided the tumor into irregular lobules.

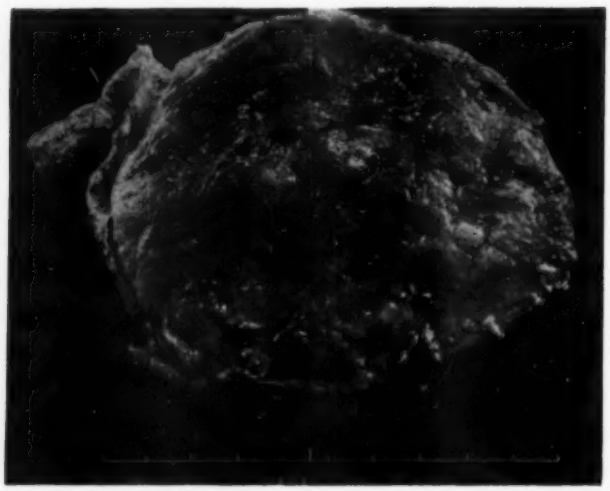

Fig. 6.—Cut surface of right adrenal tumor illustrating the encapsulation, nodularity, and bulging. Remnants of compressed adrenal are noted in the left upper corner. (From Letterman Army Hospital Medical Illustration Section. Neg. No. L6733–3.)

Microscopically the cells of the left and right adrenal tumors were essentially the same except that the cells of the right adrenal tumor showed greater pleomorphism and more hyperchromatism. Most of these cells were arranged in irregular anastomosing columns and cords with a suggestion of acinar formation in some areas. They were oval, polyhedral, and showed a pale, cloudy, abundant, eosinophilic, granular cytoplasm, with eccentric and central vesicular hyperchromatic nuclei (Fig. 7). No mitotic figures were noted. In the right adrenal tumor there were also a moderate number of very large, pleomorphic, multinucleated cells, containing eosinophilic granular cytoplasm and large pale nucleoli. Some of these nucleoli occupied almost the entire nucleus. Between some of these cells there were many small round pale eosinophilic periodic-acid-staining masses which were homogeneous and finely granular. Many of the larger cells contained pale periodic-acid-positive material in their cytoplasm. Sections of the right adrenal tumor fixed in Orth's fluid became a definite red-brown, indicating chromation. Hemotoxylin and eosin stained sections of this material showed brown cytoplasmic material in these cells. Iron stains of the tumor were negative. The tumor cells contained fine cytoplasmic granules and material which was dark brown to black with Fontana's silver stain, pale green to dark green with the Schmorl technique using Giemsa's stain as a counterstain, and yellow-green with the Schmorl technique using safranine as a counterstain. A small amount of stroma was present in the right adrenal tumor which contained large areas of hemorrhage and necrosis with collections of segmented neutrophils and eosinophils. Many fresh unorganized thrombi were present in several arterioles of the right adrenal tumor.

Bioassay of the right adrenal tumor, using the cat as a test animal, showed definite pressor activity on blood pressure and depressor activity on uterine musculature. Utilizing the method and a modification of the formula described by Goodall,[4] it contained 75 per cent epinephrine and 25 per cent norepinephrine. Preliminary studies revealed sympathomimetic substance equivalent to 6.1 mg. epinephrine per gram of tumor. Considering the weight of the right adrenal tumor this amounts to 2,318 mg. of pressor substance.

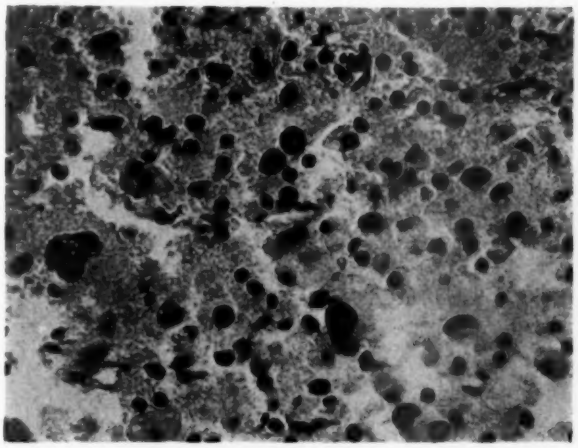

Fig. 7.—Photomicrograph of right adrenal tumor showing arrangement of irregular hyperchromatic cells with an abundant granular cytoplasm. The fine granularity of the cytoplasm is due to the chromaffin granules. High power. (From Letterman Army Hospital Medical Illustration Section. Neg. No. L6733-9.)

DISCUSSION

Although the reason for the relatively high incidence of neurofibromatosis in patients with pheochromocytoma is not clear, the work of Von Euler[5] in which norepinephrine was isolated from nerve tissue in cattle suggests that the relationship may be more than coincidence. Calkins and associates[6] reported two children with neuroblastomas, both of whom had hypertension. Extracts of the tumor in one case revealed only negligible amounts of a pressor substance, but it was pointed out that this did not necessarily rule out the possibility that the tumor may have secreted such a substance. The fact that neurofibromas, pheochromocytomas, and neuroblastomas are all of neurogenic origin suggests the possibility that there may also be a chemical or hormonal relationship between these various tumors. So far as we are aware no norepinephrine assays have been performed on biopsied neurofibromas in human beings.

During the past decade a number of clinical tests for pheochromocytoma have been developed and are widely employed in the differential diagnosis of hypertensive states. These involve observations made on blood pressure levels following the use of several pharmacologic agents. They can be divided into two groups: the so-called "provocative tests" for use in patients in whom hypertension is paroxysmal; and the use of adrenergic blocking agents in patients who have sustained hypertension. Evans and associates[7] have reported on their experience with the commonly used pharmacologic tests. They analyzed the

relative reliability of these tests in patients with proved pheochromocytomas in comparison with a group of patients with essential hypertension and with another group of patients in whom pheochromocytoma was suspected but not confirmed. Our patient had "positive" responses to the injection of histamine and Mecholyl Chloride (Figs. 2 and 3), but a marked pressor response followed the injection of benzodioxane. A similar pressor response was seen in a patient with pheochromocytoma reported by Mason[8] although the blood pressure increase was not quite so marked as in our case. A pressor response to benzodioxane has also been observed in patients with essential hypertension.[9] Although the exact mechanisms of such a response are not known, several possibilities have been suggested: stimulation of epinephrine liberation, central nervous system stimulation, and direct peripheral vasoconstriction.[10]

Thrombosis of the superior mesenteric artery has been reported to follow the injection of contrast media into this vessel on at least four occasions.[11] In our patient the development of abdominal distention, passage of bloody stools, and disappearance of peristaltic sounds led us to suspect this complication. The position of the arteriography needle tip near the origin of the superior mesenteric artery, as seen in the roentgenogram (Fig. 5), was consistent with this impression. At autopsy, however, it was found that no such accident had occurred.

Occurrence of a hypertensive crisis immediately after the performance of a translumbar arteriogram in our case strongly suggests that the procedure was at least the initiating factor in the marked hemodynamic change that preceded death. Aranow[12] has pointed out that patients with pheochromocytoma may die after slight trauma such as a minor operative procedure. MacKeith[13] mentions five patients who died following parturition or a minor operation under local anesthesia, and five other patients who died suddenly and unexpectedly in the hospital while undergoing investigation or awaiting operation. It is conceivable that the anesthesia or the trauma associated with the technique of arteriography could have been the cause of the fatal reaction in our case. It is also possible that the presence of the radiopaque media within the tumor may have stimulated an outpouring of large amounts of pressor substance into general circulation. In any event, it would seem that arteriography is a dangerous procedure in patients with known or suspected pheochromocytoma and should not be used routinely for the purpose of localizing such tumors. If it is to be used, Nelson[3] feels that such patients should be prepared by the injection of an adrenolytic agent beforehand.

SUMMARY

A case of pheochromocytoma associated with neurofibromatosis is reported. The unusually high coincidence of the two diseases is noted and the possibility of a chemical relationship between tumors of neurogenic origin is suggested. Results of diagnostic tests for pheochromocytoma are presented and discussed.

Translumbar arteriography was successful in localizing the tumor in this case, but was followed shortly by a fatal reaction. From our experience it would appear that this procedure should not be used routinely for the purpose of localizing the tumor in known or suspected pheochromocytomas.

The authors are indebted to Dr. Windsor Cutting and associates of the Pharmacology Department, Stanford University School of Medicine, San Francisco, Calif., for performing the bioassay studies on the tumor.

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Review of Recent Advances

A REVIEW OF BALLISTOCARDIOGRAPHY

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OUTLINE

I. Historical
II. Physical and Physiologic Background of Ballistocardiography
  A. Introduction
  B. Methods Used in Recording the Ballistocardiogram
    1. Types of Ballistic Systems
      a. High-frequency Undamped Systems
      b. Low-frequency Critically Damped Systems
      c. Direct-body Pickups
    2. Direction of Recording
      a. Linear (Translational) Recording Methods
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III. Clinical Application of Ballistocardiography
  A. Cardiac Output Studies
  B. The Ballistocardiogram in Clinically Normal Persons
  C. Coronary Artery Disease
  D. Other Cardiovascular Disorders
IV. Conclusions

I. HISTORICAL

THE MOVEMENTS of the body resulting from cardiovascular forces have probably been recognized for centuries, but the first effort to measure them was described in 1877 by Gordon.[1] His interest was aroused by the observation that when a man stands on a weighing machine there are regular oscillations of

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the indicator needle synchronous with the heart beat. He suspended a light platform by ropes from the ceiling, placed a man on it in the supine position, and recorded the movements of the platform. In 1905 Henderson[2] utilized a similar technique to record body motions and suggested a relationship between the magnitude of the motion and the output of the heart. Subsequently, a number of workers using a variety of instrumental approaches sought to record ballistic movements and give them physiologic meaning. Included among these are Satterthwaite,[3] Heald and Tucker,[4] Angenheister and Lau,[5] and Abramson.[6]

Despite these early efforts no real advances were made in technique or application until Starr and associates[7] reported their original investigations in 1939. Current knowledge pertaining to the fundamental physical and physiologic aspects of this method is in large measure a result of the studies Starr has conducted over the past fifteen years. He and his associates constructed a "high-frequency" bed and studied its physical properties along with those of the human body. The records from this bed were termed "ballistocardiograms." He demonstrated many of the physiologic events concerned in the production of the ballistocardiogram, developed formulas for estimating cardiac output, and, for the first time, began to carry out extensive clinical studies with the instrument. His basic endeavors and periodic reports of progress have served as stimuli to many other investigators who have since turned their attention to ballistocardiography. A radical departure in the method of recording ballistic movements was made in 1944 by Nickerson and Curtis[8] who constructed a bed with a very low frequency of vibration, capable of being critically damped. Subsequently, Dock and Taubman[9] described simplified methods of recording the ballistocardiogram directly from the body and these "direct-body pickups" have been used with increasing frequency in clinical studies.

During the last few years the scope of ballistocardiographic observation has been extended from conventional unidirectional linear recording to multidirectional "vector" ballistocardiography. Hamilton and associates[10] suggested the possibility of "vector" recording and methods have since been described by Scarborough and associates,[11] Franzblau and associates,[12] Braunstein and associates,[13] and Brandt and associates.[14] Ernsthausen and associates[15] developed a "torsion ballistocardiograph" designed to record rotational movements of the body.

II. Physical and Physiologic Background of Ballistocardiography

A. Introduction

The basic physical principle underlying the origin of the ballistocardiogram is Newton's third law of motion which states that ". . . for every action there is an equal and opposite reaction." A simple analogy to the human ballistic system would be a gun (the heart) which fires a projectile (the blood ejected by the heart) through a U-shaped barrel (the aorta), the whole system being mounted on a soft rubber pad. When the gun is fired there is an immediate recoil in a direction opposite to that of the projectile. Shortly thereafter the projectile reaches the curve in the barrel (aortic arch) which arrests its progress and reverses

its direction. This impact brings an end to the initial recoil motion (the I wave) and moves the whole system in the opposite direction (the J wave). In order to complete the analogy, the gun barrel must be narrowed at the muzzle (bifurcation of the aorta). Thus, when the projectile reaches the narrow portion of the barrel it is suddenly slowed, producing an impact which cancels the previous motion and again moves the system in the opposite direction (the K wave).

B. METHODS USED IN RECORDING THE BALLISTOCARDIOGRAM

1. *Types of Ballistic Systems.*—Recognition that the body is driven by forces set up in the cardiovascular system posed the problem of selecting suitable methods for recording the motions. One of the most important requirements in the design of recording systems is that the natural frequency of the instrument should be far removed from the frequency of the phenomenon being recorded. The natural frequency of the human body, whether driven from within by cardiovascular forces or from without by applied impacts, varies between 3 to 7 cycles per second in different subjects and averages about 5 cycles per second. Therefore a system designed to record the human ballistocardiogram should have a natural frequency well outside of this range, otherwise resonance between the body and the recording system may result in a completely distorted representation of body motions. This fact was given consideration in the development of the high- and low-frequency beds, for in each case the natural frequency of the instrument is outside the range of body natural frequencies.

The ballistic systems which have been employed in recording the human ballistocardiogram are of three general types: (1) high-frequency undamped systems, (2) low-frequency critically damped systems, and (3) devices applied directly to the body which have no externally applied damping or restoring force other than that produced by the coupling between the body and the rigid surface upon which it rests. Detailed discussion of the relative merits and physical properties of these three systems is beyond the scope of this review; the reader is referred to the works of Starr, Nickerson, and Dock for details.

a. *High-frequency Undamped Systems.*—All bed ballistocardiographs, whether of high or low frequency, are similar in basic design. They consist of a light rigid rectangular platform suspended from above or supported from below and usually constrained in such a manner that motion is possible in only one direction. The platform is attached to one or more steel springs which determine its natural frequency and supply its restoring force. The major difference between high- and low-frequency beds is in the character of these springs. In the construction of a high-frequency bed very stiff springs are employed to give the system a high natural frequency and great rigidity. The original high-frequency bed designed by Starr and associates[7] was suspended by cables from the ceiling and connected to a short stiff steel spring attached to the floor. The movements of the platform were magnified about 7,000 times by an optical system and recorded on a strip of moving film. Since this original high-frequency ballistocardiograph, a variety of designs have been used in the construction of beds of this type. Fig. 1,*A*, shows a high-frequency ballistocardiograph now being produced commercially.* In this case the mechanical motion of the platform is converted to electrical energy (by an electronic transducer) which is amplified and used to drive a recording instrument.

*Manufactured by the Technitrol Engineering Co., 2750 N. 4th St., Philadelphia 33, Pa.

The term "high frequency" refers to the fact that such a bed has a high natural frequency of vibration when the platform is excited by an impact. Loaded with 150 pounds dead weight (iron or steel) its natural frequency is usually between 10 and 15 cycles per second. The degree of damping, that is, the rapidity with which the oscillations cease after a single impact, depends on the mechanical characteristics of the whole system which includes the supporting structure, the platform, and the mass on the platform. When the bed is loaded with dead weight there is little damping in the system; after an impact it continues to oscillate for an appreciable period of time. On the other hand when the dead weight is replaced by an elastic viscous mass, such as a human cadaver, both frequency and damping are changed. An impact on the head of the

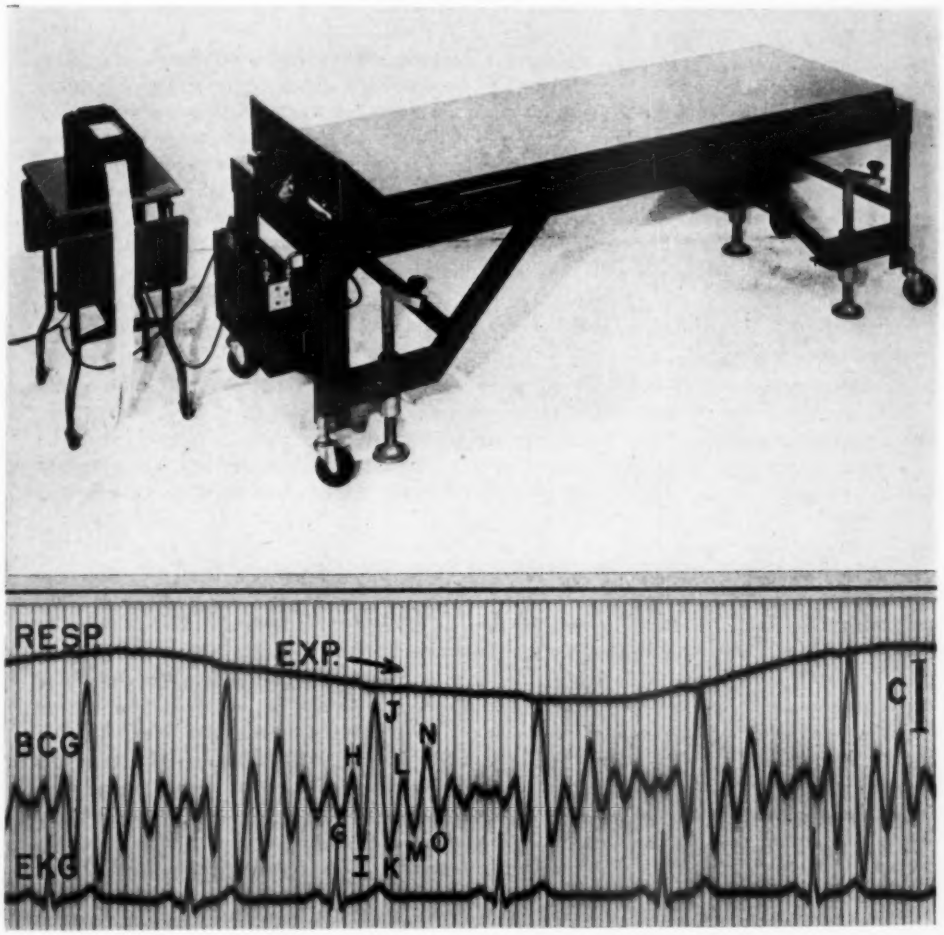

Fig. 1.—*A*, High-frequency ballistocardiograph, commercial model. This instrument has a natural frequency of 12 to 14 cycles per second when loaded with 150 pounds dead weight. The electronic transducer and amplifier are mounted on the foot end of the frame. (Courtesy Technitrol Engineering Co.)

B, Normal ballistocardiogram recorded with a high-frequency bed. The upper tracing (*RESP*) is the pneumogram (expiration downward), the middle one (*BCG*) is the ballistocardiogram, and the lower one is the electrocardiogram (Lead II). Heavy time lines are 0.1 second apart. The bracketed vertical line (*C*) in the upper right corner represents the calibration deflection (280 Gm. = 1 cm.).

This record obtained during normal breathing shows the usual decrease in ballistic amplitude during expiration and the increase during inspiration. The base line is unaffected by respiration. Note that all complexes are similar in wave form. The waves are labeled according to Starr's convention. Downward deflections represent footward body movements.

cadaver produces low-frequency oscillations (around 5 cycles per second) which are very rapidly damped out. Both the frequency and damping of the oscillations produced in this manner are similar to those produced when the cadaver, lying on a rigid surface, oscillates on its own tissues. This suggests that the body itself dominates the bed-body system and that the motion recorded by the bed is a reasonably faithful qualitative reproduction of body motion. However, the restraint imposed by the stiff spring does not allow the bed to reproduce the actual magnitude of body motion since the motion of the body with respect to the platform is several times larger than the motion of the platform with respect to the fixed base.

The sensitivity of the high-frequency bed is standardized by static mechanical calibration. The amplification is so adjusted that a standard force (280 grams' weight) applied to the end of the bed produces a standard deflection (1 cm.). It is not necessary to calibrate for each subject since calibration is largely independent of the mass on the bed.

Fig. 1,*B*, shows a normal ballistocardiogram recorded with a high-frequency bed. The electrocardiogram supplies a cardiac "timer" and the pneumogram indicates the phase of respiration. Although the amplitude of the ballistocardiographic complexes varies during the respiratory cycle, the base line remains straight and undistorted. The ballistic waves are labeled according to Starr's convention. The H wave is a small, somewhat variable, headward wave often preceded by a smaller footward wave which has been termed the G wave. The sharp footward I wave is followed by the headward J wave which is usually the largest of the ballistic waves. The footward K wave occurs in late systole and is usually slightly deeper than the I wave. The L, M, N, and O waves are in diastole and are normally much smaller than the systolic waves. The ballistocardiograms of young normal subjects are quite similar in appearance and the wave form is highly reproducible in the same individual. Table I gives the normal values for some of the wave amplitude ratios and time intervals.[16]

b. *Low-frequency Critically Damped Systems.*—Nickerson and Curtis[8] chose to build a bed with a natural frequency lower than the natural frequency of the human body. Their bed consists of a light, rigid platform supported at its four corners by long steel cantilever springs fixed to the base. The effective spring length can be altered by an adjustable clamping device. The platform is connected by a rod to a damping system which permits the degree of damping to be adjusted for any bed load.

The low-frequency bed was designed to permit observation of the early systolic events but to minimize those in diastole; this design was selected because Nickerson's primary objective was the determination of stroke volume from the initial ballistic impacts. He chose as the ideal case a system which, offering no restraint to body motion, would allow the body and bed to move in perfect unison. His work led him to the view that true records of body displacement are obtained only when the bed frequency is below 1 cycle per second and that the lower the bed frequency the more faithfully are body motions reproduced. However, with bed frequencies below 1 cycle per second, it was necessary to suspend respiration in order to obtain records; this procedure considerably alters normal cardiodynamic conditions which exist during breathing. The operating conditions which were finally chosen, namely, a bed frequency of 1.5 cycles per second with critical damping, were believed to be a convenient compromise. Under these circumstances quiet breathing is permissible and, although amplitude is reduced and the wave form altered, the errors involved are believed to be small. Even with quiet breathing, however, there is considerable base line movement.

Fig. 2 shows a Nickerson low-frequency ballistocardiograph* with a typical normal ballistocardiogram inscribed during suspended respiration. The records obtained from the low-frequency bed are roughly similar to those from the high-frequency bed. Both show H, I, J, and K waves but the J and K waves in records from the Nickerson bed occur much later than the corresponding waves in high-frequency records. Table I gives normal values for some of the wave amplitude ratios and time intervals for low-frequency records as published by Jones and Goulder.[17] The low-frequency bed is calibrated by applying a force of 35 or 40 grams to the platform during a portion of the tracing, the force being provided by weights hanging over a light frictionless pulley. The bed is adjusted for each subject's weight so that in all cases the bed frequency is 1.5 cycle per second and damping is critical.

*Manufactured by the National Bent Steel Corp., 53-01 Nurge Ave., Maspeth, Long Island, N. Y.

TABLE I. MEASUREMENTS FROM NORMAL BALLISTOCARDIOGRAMS

	SUBJECTS			TIME INTERVALS (IN SECONDS)								AMPLITUDE RATIOS (IN PER CENT)			
				Q-H		Q-I		Q-J		Q-K		HI/IJ X 100		JK/IJ x 100	
	NO.	AGE (YRS.)	SEX	MEAN	S. D.	MEAN	S. D.	MEAN	S. D.	MEAN	S. D.	MEAN	S. D.	MEAN	S. D.
A. High-frequency ballistocardiogram[16]	155	20-69	M	0.108	(0.02)	0.175	(0.02)	0.251	(0.02)	0.342	(0.02)	—	—	107	(10.2)
	70	20-69	F	0.105	(0.02)	0.172	(0.01)	0.241	(0.01)	0.330	(0.02)	—	—	103	(9.8)
B. Low-frequency ballistocardiogram[17,120]	40	17-37	M&F	0.136*	(0.01)	0.213	(0.02)	0.375	(0.02)	0.581	(0.04)	38	(8)	105	(20)
	39	38-85	M&F	0.138*	(0.02)	0.203	(0.03)	0.351	(0.03)	0.541	(0.04)	31	(14)	114	(37)
				R-H		R-I		R-J		R-K					
C. Direct body ballistocardiogram Electromagnetic[19] (unfiltered)	75	20-30	M	0.08	(0.01)	0.14	(0.01)	0.21	(0.01)	0.30	(0.02)	52	(6)	128	(8)
	25	20-30	F	0.07	(0.01)	0.13	(0.01)	0.19	(0.01)	0.27	(0.02)	47	(4)	133	(9)

*Twenty-five subjects.

c. *Direct-body Pickups.*—The direct-body pickups, which were introduced by Dock and Taubman,[9] are much simpler in principle than the bed ballistocardiographs. They are designed to record the motion of a bar or crosspiece laid across the shins of the patient, who lies supine on a rigid table. There is no restraint, restoring force, or damping other than that supplied by the coupling of the body to the tabletop. These devices are of two general types: (1) velocity measuring pickups (for example, electromagnetic), and (2) displacement measuring pickups (for example, photoelectric or piezoelectric[13]). Records from the displacement pickups are similar in timing and wave form to those from high-frequency beds. Since velocity is the derivative (differential) of displacement, the waves from the velocity pickup records are 90 degrees out of phase with those of displacement records, the peaks of the waves in velocity tracings occurring earlier than the corresponding waves in displacement records. Fig. 3,*A*, shows a commercially available direct-body ballistocardiograph* set up for routine operation. (This particular instrument includes

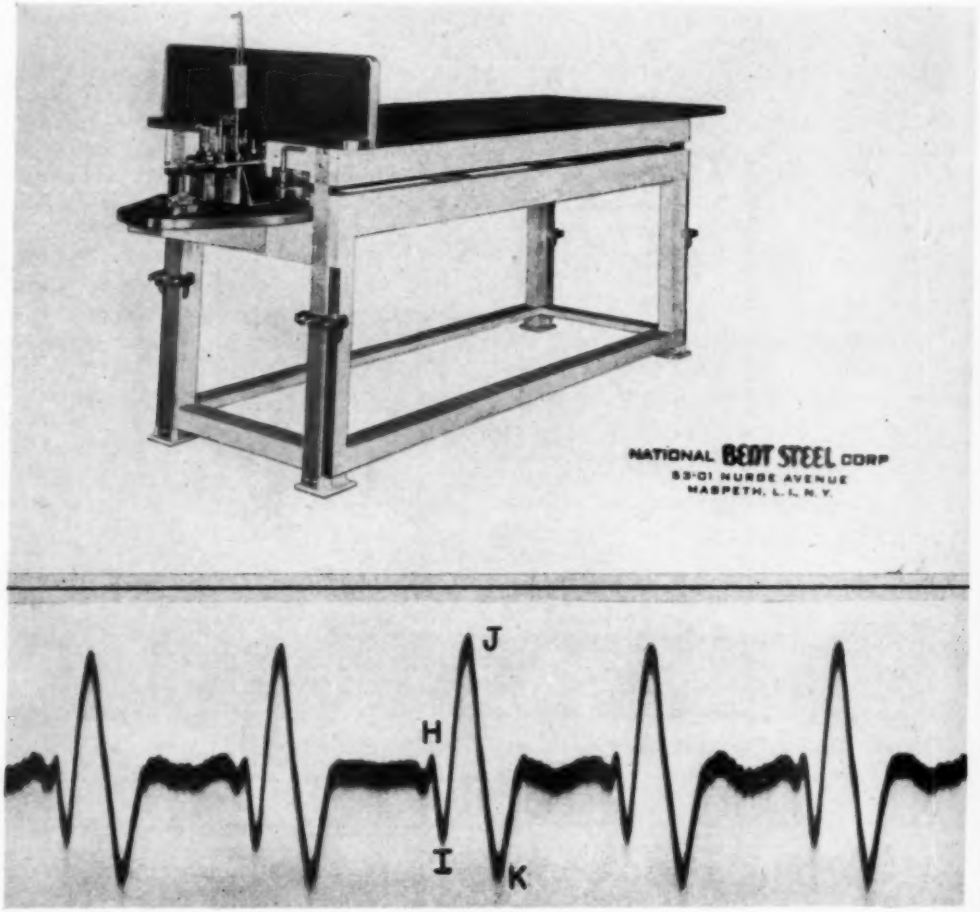

Fig. 2.—*A*, Low-frequency ballistocardiograph, commercial model. The upper platform of this bed is supported by four long, flat steel springs. Both damping and frequency are adjustable. The damping apparatus and the transducer are mounted on the foot end of the frame. (Courtesy National Bent Steel Corp.)

B, Normal ballistocardiogram recorded with a low-frequency bed during suspended respiration. Although the systolic waves in low-frequency ballistocardiograms are considerably later in time than those in high-frequency records, they are designated by the same letters.

*The Pordy Dual Ballistocardiograph, manufactured by the Mendelsohn Research Laboratories, Inc., 15 Maiden Lane, New York 38, N. Y.

both photoelectric and electromagnetic pickups.) Examples of simultaneous displacement and velocity records are shown in Fig. 3,*B*. Table I gives the normal values for certain time intervals and wave ratios obtained from velocity (electromagnetic, unfiltered) records by Smith and Bryan.[19] Records from young normal persons taken by velocity and displacement pickups are similar in form. The displacement records show rhythmical undulations of the base line due to movements of the body on its fat pad during the respiratory cycle. Most of the displacement pickups include filters designed to eliminate these low-frequency respiratory movements, but they tend to produce some alteration in the timing and form of the waves. Records taken with the velocity pickups show straight base lines, uninfluenced by quiet respiration. If suitable condensers are used with

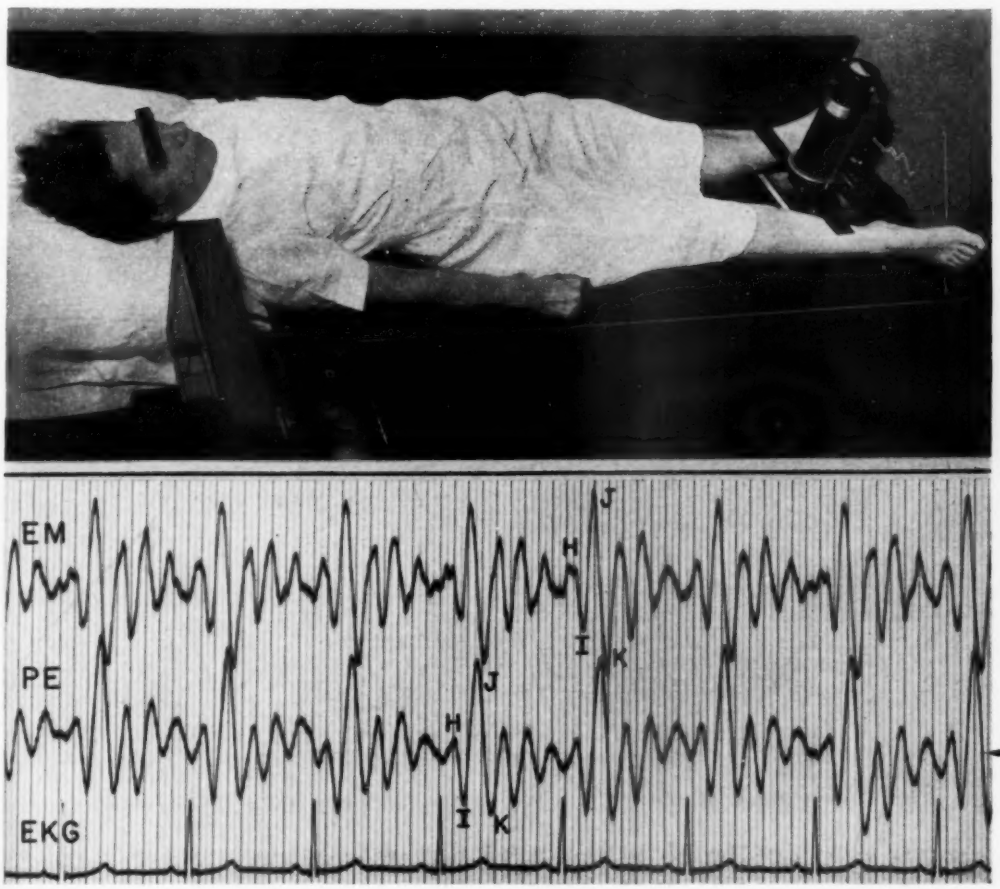

Fig. 3.—*A*, Direct-body ballistocardiograph, commercial model. This instrument is so designed that photoelectric (displacement) and electromagnetic (velocity) records may be taken from the same shin crosspiece. During ordinary breathing the base line of the electromagnetic tracing remains straight, but the photoelectric base line shifts rhythmically with respiration. If desired, a filter may be switched in to reduce the base line shift. Provision is also made for superimposing an electrocardiographic lead onto either of the ballistocardiographic records. (Courtesy Mendelsohn Research Laboratories.)

B, Simultaneous direct-body ballistocardiograms recorded during suspended respiration. These records were taken with the instrument shown above (a minor alteration was required to record the two tracings simultaneously). The electromagnetic tracing above (*EM*) was taken with a condenser removed and represents true body velocity. The photoelectric tracing below (*PE*) was recorded without filters and represents true body displacement. Note that the tips of the waves in the electromagnetic tracing precede those in the photoelectric tracing. The two curves are 90 degrees out of phase. Heavy time lines are 0.1 second apart.

this apparatus, there is electrical integration so that the velocity record is converted to one of displacement. For timing purposes the electrocardiogram may be superimposed on the ballistocardiogram by mixing the two signals;[20] independent gain controls permit the electrocardiogram to be kept small enough so that it does not distort the ballistocardiogram but large enough to produce identifiable R waves preceding the ballistic H waves. No adequate method for mechanical calibration of the velocity or displacement pickups has been described and for this reason only the qualitative appearance of the tracing is taken into consideration.*

2. *Direction of Recording.*—Theoretically, a body has six independent degrees of freedom, three of these being translations and three rotations. The translations represent straight-line movements along the three spatial axes and the rotations represent angular movements about the same three axes. While the designers of ballistic systems have been primarily concerned with the recording of linear (translational) body motions along the longitudinal axis there is evidence that all six motions are participated in by the human body.

a. *Linear (Translational) Recording Methods.*—

(1) *Unidirectional recording*: The high- and low-frequency beds and the direct-body pickups are used principally to record the longitudinal (head-foot) ballistocardiogram with the subject in the supine position. Methods have also been described for recording the longitudinal ballistocardiogram from patients in the sitting and standing (vertical) positions.[4,6,21,22] By using a tilt table, records may also be taken at any angle between the vertical (standing) and horizontal (supine) positions.[22] The records obtained by these techniques differ from the usual supine record in only minor details, although Krahl[22] noted splitting of the I wave in his standing records. In most normal subjects the systolic waves are smaller and the diastolic waves are larger in the standing records than in the supine records. Although the vertical ballistocardiographs thus far described are all high-frequency instruments, respiration causes considerable shift in the base line. There is also more distortion due to muscular tremor and building vibration.

(2) *Multidirectional recording methods*: The recognition that human ballistic movements are not confined to the longitudinal (head-foot) axis has led to the development of new techniques for recording motions in other directions. In 1945 Hamilton, Dow, and Remington[10] published a diagram redrawn from tracings made with a bed system capable of recording simultaneously the three body translations (head-to-foot, side-to-side, and front-to-back). The details of the construction and design of this instrument were not published and the authors have not extended their observations on the spatial orientation of human ballistic movements.

A modification of the ballistocardiograph bed permitting observation of movement along any axis in the frontal plane of the body has been described by Scarborough and associates[11] (high-frequency bed) and by Franzblau and associates[12] (low-frequency bed). This modification involves the use of a light turntable mounted on top of the bed which allows rotation of the body about a central pivot. Records may be taken along the longitudinal (head-foot) and transverse (side-to-side) axis or along any other axis in the frontal plane. In addition, tracings may also be obtained of motions along the anteroposterior axis of the body. Records from both high- and low-frequency beds reveal the same type of vector loop pattern (constructed). The I wave is footward, to the right, and anterior; the J wave is headward, to the left, and posterior. Turntable records from patients with normal and abnormal head-foot ballistocardiograms have been published.[11] Although the turntable method is a simple one, the "vector" records cannot be taken simultaneously and this constitutes a distinct disadvantage.

Braunstein, Oelker, and Gowdy[13] have designed and constructed a high-frequency ballistocardiograph with two degrees of freedom, making possible the recording of simultaneous longitudinal and transverse ballistocardiograms. The transverse motions are recorded at three points

*Dr. J. E. Smith, (Medical Standards Branch, Civil Aeronautics Administration, Washington) has recently submitted for publication a paper describing a method for calibrating electromagnetic pickups.

along the side of the bed, one near the head, one at the center, and one near the foot of the bed. The transverse records from the head end are quite similar to the transverse (lateral) turntable tracings. The use of the three transverse pickups has demonstrated that the body rotates about a vertical (anteroposterior) axis since the foot-end component is usually a reciprocal of the head-end component. It is clear, therefore, that the transverse pickups record a mixture of both translation and rotation. Braunstein[24] has made photographs of the frontal vector loop (using the longitudinal and head-end transverse pickups) from the face of an oscilloscope, a technique similar to that used in vectorcardiography.

Brandt and associates[14] have recently described a method for recording body motions simultaneously in three directions by utilizing the electromagnetic pickup devised by Dock. The longitudinal record is taken in the usual manner from the shins. Transverse and dorsoventral records are taken by recording directly the motion of the right lateral and right anterior chest walls with electromagnetic pickups. The method differs from those previously referred to in that local motion of the thorax is recorded rather than motion of the body as a whole. In most cases tracings from the right lateral thoracic wall showed a leftward motion synchronous with the I wave and a rightward motion synchronous with the J wave. This pattern is similar to Hamilton's but differs from that obtained with turntables and two-directional beds. Brandt suggests that the differences may be due to the effects of rotation of the body about one or more axes when bed methods are used. This point seems well taken but further work is needed to clarify the effects of rotation.

b. *Angular (Rotational) Recording Methods.*—With all the methods described above the primary object was to record one or more translations (linear motions) and to exclude as nearly as possible the rotations. However, Ernsthausen, Reismann and their associates[15, 25] have described a ballistocardiograph designed to record rotations and to exclude translations. The principal feature of this instrument is a rigid tabletop supported by wires from above and attached to a torsion bar or spring located beneath the geometric center of the tabletop. The bed is so designed that only rotational movements about the vertical torsion bar are recorded. Motions along axes running through the center of rotation are not recorded. When a subject is placed in the supine position on the table top so that the center of rotation is through the midabdomen, the record obtained depicts the angular momenta applied to the torsional system by the body. The curves show an initial counterclockwise rotation (viewed from above), which begins shortly after systolic ejection, and is followed by a smaller clockwise rotation, another counterclockwise rotation, and then a series of smaller oscillations. The first three large rotational waves seem to correspond in time to the I, J, and K waves of the conventional high-frequency head-foot ballistocardiogram. This method has several interesting possibilities one of which is that forces produced in one part of the circulatory system may be separated from those produced in another part. The reader is referred to the work of Ernsthausen and associates[15] for theoretical considerations, experimental evidence, and construction details relating to this method.

It is still too early to draw any definite conclusions with regard to the ultimate value of multidirectional ballistocardiography. The factors responsible for the spatial distribution of body movements have yet to be clarified. It is clear, however, that multidirectional recording offers more and different information about circulatory dynamics than can be obtained from the conventional longitudinal records alone. The advantages to be gained might be likened to those of using the three standard limb and precordial electrocardiographic leads over the use of a single limb lead.

C. ORIGIN OF THE BALLISTOCARDIOGRAM

1. *Physical Properties of the Human Body.*—Before reviewing the experimental work relating to the forces produced within the cardiovascular system, it is advisable to consider briefly the physical properties of the human body which play a role in the transfer of energy from the circulatory system to the externally placed recording instrument. These properties are of great importance for they may modify to a large extent the internal forces applied to the body. Unfor-

tunately there is very little precise information available on this subject. There are the obvious anatomic facts that the heart and aorta are loosely coupled to the spine, that the spine is coupled to the rest of the bony framework, and the bony framework is coupled (by connective tissue, muscle, fat, and skin) to the surface on which the body rests. The physical characteristics and variability of these multiple couples are unknown. The body is a viscous elastic mass and its natural frequency is low, varying from 3 to 7 cycles per second in different subjects.[7,26] It is highly damped but not critically damped, since after being displaced, it oscillates back and forth several times before coming to rest. It is clear that the body acts as a "low-frequency recorder" and is therefore probably incapable of faithfully following rapid phenomena arising within it. This is an "error" which must be accepted by those using the existing types of ballistocardiographs. It should be borne in mind that if the relationship of body and bed is modified (by footboards, headboards, skeletal fixation, etc.) the responses of the system to impressed forces will also be modified. Therefore, ballistocardiograms recorded directly from the unconstrained body will not be identical with those recorded from a bed to which the body is firmly fixed.

2. *Forces Produced by Cardiovascular Events.*—The simple analogy between the human ballistic system and a gun resting on a rubber pad is a convenient way of visualizing the mechanics involved in the production of the ballistocardiogram, but it is, of course, a great oversimplification. There is not only one gun but two, represented by pulmonary and systemic arterial trees. The two "barrels," the aorta and pulmonary artery, are not rigid barrels but elastic tubes which branch and change caliber. There is a continuously flowing fluid column instead of a single projectile.

In the original paper on the ballistocardiogram, Starr and associates,[7] calculated the force produced during a single cardiac cycle in man. This calculation required an acceleration factor, since force is equal to the product of mass and acceleration. Inasmuch as neither velocity nor acceleration of blood flow in the human aorta is known, it was necessary to utilize a velocity curve recorded by Machella[27] from the aorta of a dog and to assume that it applied to the human being and to the pulmonary artery as well as the aorta. From the velocity curve its derivative, acceleration, was obtained and by multiplying the acceleration at each instant in time by the mass of blood involved, a curve was plotted representing the total force produced. This curve was found to be roughly similar to the normal ballistocardiographic complex recorded with a high-frequency bed.

In a later paper Starr and Rawson[21] reported a similar but more detailed study of the forces produced by the flow of blood in the right and left sides of the heart, the pulmonary artery, and the aorta. They concluded that the major force contribution was from aortic blood flow whereas that from pulmonary artery flow was small. The I wave was found to result from blood flow within the heart and aorta while the J wave resulted almost entirely from aortic flow.

In 1945, Hamilton and associates[10] reported the results of a study on the relationship between the cardiac ejection curve and ballistocardiographic forces. Like Starr they calculated a theoretical force curve but they used somewhat different methods to do so. Instead of using the ejection velocity curve from a

dog, they derived an ejection curve from a normal human being by the pressure pulse contour method.[28] A calculation was made of the forces produced by the ejection of blood from the heart and its flow through the aorta and pulmonary artery. The summated force pattern was compared with the high- and low-frequency ballistocardiograms and two major discrepancies were found. One of these was that the beginning of the I wave of the ballistocardiogram is delayed about 20 milliseconds after the beginning of ejection. Hamilton was not able to explain this delay by the manner in which the forces are transmitted or recorded. Evidence was presented suggesting that the movement of venous blood and of the heart itself during early systole (isometric contraction) produces a headward force which partially cancels the initial footward recoil, delaying the beginning of the I and reducing its amplitude. It was suggested that this canceling headward force might account, in part, for the H wave. The second discrepancy between the ballistocardiogram and the calculated force curve was in amplitude. This was believed to be due to the initial canceling headward force, to loss of energy in overcoming momentum, and to the effects of viscous frictional resistance. There is some question as to the validity of the calculated ejection curves and of the force curves derived from them. (See section on Cardiac Output.)

The fundamental studies by Starr and Hamilton make it clear that both the contour and the amplitude of the ballistocardiogram are related to the cardiac ejection curve. In his original theoretical treatment Starr pointed out that, when the ejection velocity curve departed from normal, the resulting ballistocardiogram should also be abnormal. By assuming various types of abnormal velocity curves he derived different abnormal ballistocardiographic patterns, some of which are seen in the records from patients with heart disease. More recently, Starr and associates[29] have devised a technique which permits direct comparison of the cardiac ejection curve with the ballistocardiogram. This technique involves the injection of fluid, in controlled and measured quantity and rate, into the aorta and pulmonary artery of a fresh cadaver while the "ballistocardiogram" is recorded. The method therefore simulates the pumping action of the heart. In Starr's hands this injection technique has clarified some of the relationships between cardiovascular forces and the ballistocardiogram. Although the results of these studies cannot be considered in detail here, a few of the more pertinent findings should be pointed out. One of the simplest and most important observations was that the size and shape of the cadaver ballistocardiogram depended on the force used in ejecting fluid into the great vessels. Mathematical treatment of the ejection curves and the cadaver ballistocardiograms led Starr to the conclusion that the ballistocardiogram is related to the third derivative of the ejection curve, which represents the rate of change of force. When the ejection curve was differentiated three times it resembled the ballistocardiogram and, conversely, when the ballistocardiogram was integrated three times, it resembled the ejection curve. The resemblances were not perfect, which is probably due partly to the U-shape of the aorta. The ballistocardiogram is not an exact reproduction of the third derivative of the ejection curve but is rather the algebraic sum of two third derivatives of the curve of opposite signs, one placed a little before the other in time.

Although it is possible to derive the cardiac ejection curve (and therefore cardiac output) by integrating the ballistocardiogram three times, the use of this method for estimating cardiac output quantitatively is difficult to apply and is subject to large errors. Since his results revealed that the ballistocardiogram is more closely related to the heart's force than its output, Starr then chose to devise methods for estimating the strength or force of cardiac contraction. The first integral of the ballistocardiogram (area of the I and J waves) was shown to be closely related to *total* cardiac force. However, he found an even closer relationship between I-J amplitude and *maximum* cardiac force and chose to utilize this relationship in estimating cardiac force from the ballistocardiogram. Normal standards based on findings in 100 healthy subjects of both sexes from 20 to 39 years of age were set up and regression equations relating I-J amplitude to surface area were calculated.[29*]

On the basis of the studies previously referred to, Hamilton and associates[10] described the probable origin of the various ballistic waves. The *H wave* was ascribed to the footward movement of the heart during isometric contraction. The *I wave* was believed to represent the remainder of the (partially canceled) footward thrust developed during the ejection of blood into the aorta and pulmonary artery. The *J wave* was ascribed to the deceleration of blood in the heart, ascending aorta, and pulmonary artery and to the acceleration of blood in the descending aorta. The *K wave* was thought to be a footward thrust resulting from the impact and reflection of the pulse wave at the periphery of the arterial tree. The *L wave* was ascribed to the deceleration of blood in the ascending aorta at the end of systole, reinforced by a transient reversal in the direction of flow. This reversed wave sharply closes the aortic valve and again changes directions, producing a footward thrust; coupled with deceleration of flow in the descending aorta, this brings an end to the L wave and produces the *M wave*. The *N wave* could not be accounted for by any physiologic phenomenon and was therefore believed to be "afterfling," but the *O wave* was ascribed to a reflection of the pulse wave at the periphery.

Nickerson[30] has reported the results of a series of studies on the origin of the H and K waves of the low-frequency ballistocardiogram. Using a mechanical heart-aorta model he showed that the depth of the K wave is related to the length of the aorta. Shortening of the aortic length produced a decrease in the depth of the K wave. By constricting the model "aorta" at its arch he caused the K wave to disappear, thereby producing a pattern similar to that seen in patients with coarctation of the aorta. The induction of reactive hyperemia in the lower extremities of normal subjects was also found to decrease the depth of the K waves, presumably by decreasing vascular resistance. With respect to the origin of the H wave, Nickerson presented evidence suggesting that the H wave represents an impact produced by auricular contraction and showed that this impact delays the onset of the I wave. There is now considerable evidence supporting Nickerson's contention that auricular contraction produces ballistic deflections and is involved in the production of the H wave.[26,32] In most cases of

*Recent evidence indicates that there is no significant correlation between I-J amplitude and surface area when men and women are considered separately.[16]

complete heart block there are distinct auricular complexes following each P wave. The H wave of the ventricular complex under these circumstances is usually absent unless the interval between the preceding P wave and the QRS complex is within normal limits, in which case G and H waves may be evident. In normal ballistocardiograms there is a significant correlation between the Q-H (beginning of electrocardiographic Q wave to peak of ballistic H wave) and the P-R intervals suggesting a relationship between auricular activity and the H wave.[16] In addition, it is usually possible to separate the body motions responsible for the H wave from those producing the IJK waves by recording "vector" ballistocardiograms.[31] However, deflections resembling H waves are at times present in records from patients with auricular fibrillation, a condition in which there is no forcible auricular contraction. It seems likely, as de Lalla and associates[32] suggest, that both auricular contraction and the thrust of the heart during isometric contraction are concerned in the origin of the H wave.

D. FORM OF THE BALLISTOCARDIOGRAM

The general form of the normal ballistocardiographic complex has already been commented on. As yet no criteria of normality for the form of the individual ballistocardiographic complex have been agreed upon. The importance of the cardiac ejection curve in determining the size and shape of the ballistocardiographic complex has already been considered. By varying cardiac ejection in cadaver experiments Starr and associates[29] were able to simulate normal ballistocardiograms and most of the types of abnormal ballistocardiograms obtained from living patients. It is evident that ballistic form abnormality may result from abnormal cardiac ejection due to "weakness" of cardiac contraction, and this mechanism is probably responsible for the abnormal ballistocardiograms from many patients with overt cardiac disease. There is, however, some reason to believe that certain extracardiac factors may be operative in the production of ballistocardiographic abnormality. The effects of changes in aortic elasticity, lung elasticity, and the pulmonary circulation and the influence of peripheral and splanchnic blood pooling have been speculated on but have not been fully clarified.

1. *Systolic Abnormalities.*—In early clinical studies with the high-frequency bed, Starr and Schroeder[33] described three varieties of abnormal systolic complexes and called them "early M," "late M," and "late downstroke" types. They also noted records in which there were intermediate types of abnormal complexes and still others in which there was no consistent wave form. The "early M" form, which is probably the commonest type of abnormal complex, is characterized by a tall H wave, a short or absent I wave, and a low, rounded J wave. The "late M" form, relatively uncommon, shows a doubled J wave. The "late downstroke" form, intermediate in frequency, shows little or no I wave, a low rounded J wave, and a deep K wave. None of these patterns appears to be characteristic of any specific type of cardiovascular disease and more than one type may occur in the same ballistocardiogram. Aside from these types, other systolic abnormalities have been noted. Complexes with very deep K waves (and often short I waves) have been noted commonly in the records (high- and low-frequency and direct-body) from patients with hypertension and with aortic

insufficiency.[17,34-36] A probable reason for the deep K wave in hypertension is that the increased peripheral resistance produces a more abrupt deceleration of blood at the bifurcation of the aorta and hence a greater footward impact. The depth of the K wave has been seen to decrease when the elevated blood pressure was lowered by hypotensive drugs.[23] A similar decrease has been noted in records from patients in shock.[37] Jones and Goulder[17] have found that the peaks of the I and J waves appear earlier than normal in the low-frequency records from patients with hypertension. This may be due to the increased pulse wave velocity in hypertension. The cause of the deep K wave in aortic insufficiency has not been fully clarified. In the low-frequency record the peak of the K wave occurs in early diastole, so the deep K wave in this type of record may be related to the regurgitation of blood into the ventricle. No such mechanism can be postulated for the high-frequency record in which the peak of the K wave occurs before the beginning of diastole.

Absence of the K wave may be found in both high- and low-frequency ballistocardiograms from patients with coarctation of the aorta. Attention was first called to this pattern by Hamilton and associates.[10] Nickerson[30] published tracings showing the characteristic absence of the K wave and conducted experimental work bearing on the origin of the pattern. The constriction at the aortic arch prevents the high-velocity blood flow down the aorta and eliminates the sharp impact due to deceleration at the aortic bifurcation. Following a successful end-to-end aortic anastomosis the K wave usually reappears.[31,38] It has been pointed out by Jones and Goulder[17] that although short K waves are present in association with other conditions (notably vertical hearts) a *delayed* and short or absent K wave in the low-frequency record is characteristic of aortic coarctation. The pattern seems to be present in most, if not all, patients with coarctation when studied with the low-frequency bed but is absent in some high-frequency records for reasons which are not clear.[26] The absent K pattern has also been seen in low-frequency records from cases of thrombosis of the abdominal aorta.[39,40] It has been postulated that the K wave is absent in this condition because the deceleration of the abdominal aortic blood occurs earlier than usual and that the impact produced by it is canceled by the headward thrust responsible for the J wave. Why obstruction of the lower abdominal aorta should produce a pattern similar to that of obstruction at the aortic arch is not evident.

Other nonspecific abnormalities of the systolic waves are common in records from high-frequency beds and direct-body pickups. There may be slurring or notching of the H-I, I-J, and J-K segments or rounding, flattening or doubling of the I, J, or K peaks. Little has been published on the types of form abnormality in records from low-frequency beds.

2. *Diastolic Abnormalities.*—Abnormalities occurring in diastole are not uncommon in high-frequency records but such diastolic impacts are usually damped out in those from the low-frequency bed. Although abnormally tall L waves have been described in rheumatic carditis or mitral stenosis,[37] for the most part the abnormal diastolic impacts cannot be definitely identified as exaggerated normal diastolic waves. They appear to be associated with abnormal ventricular filling since they usually occur in patients with heart failure, gallop rhythm, and

constrictive pericarditis.[9,32,41] It seems likely that these abnormal waves are produced by a rapid surge of blood under high pressure into "atonic" ventricles. These waves may occupy all of diastole or may be confined to early or late diastole as is often the case in gallop rhythm wherein the gallop sound coincides in time with the ballistic waves.[42,43] When abnormal diastolic waves begin in late diastole they frequently "ride into" and distort the early systolic waves. These waves are at times more easily demonstrable in "vector" records than in head-foot records.[41]

While no normal standards or system of classification for the form of the individual ballistocardiographic complex have been published, Brown and associates[44] suggested a method for classifying abnormal high-frequency ballistocardiograms into four groups depending on a qualitative evaluation of ballistic form and on the magnitude of respiratory variation. A method for classifying low-frequency ballistocardiograms has not been published, but Jones and Goulder,[17] believes that the timing of the systolic waves may be of importance in determining the normality of such records.*

E. DETERMINATION OF CARDIAC OUTPUT

Much of the early interest in the ballistocardiograph centered about its use as a means of estimating cardiac output. A number of investigators, using both high- and low-frequency beds, have sought to establish its value in such an application. This section will deal with the validity and reliability of the methods used in calculating cardiac output.

Since the high- and low-frequency beds are different physical systems and since different methods are used in calculating cardiac output from their records, they will be treated separately. It should be pointed out, however, that the calculation of cardiac output is based on the same principle in either case, that is, that the force produced by the ejection and flow of blood is related to stroke volume. If the force produced does not bear a predictable relationship to stroke volume then it makes little difference how the force is measured, whether by a high- or low-frequency bed, as far as the estimation of stroke volume is concerned. This appears to be one of the major errors involved in ballistocardiographic methods for, since force is equal to the product of mass (stroke volume) and acceleration (of blood from the heart), one must assume that acceleration is relatively constant in the same individual and from one person to the next. Ejection velocity (and its derivative, acceleration) has never been measured directly in the human being so its absolute value must also be assumed. With the possible exception of Hamilton and Remington's pressure pulse method,[28] which requires aortic blood pressure curves, there is no way of ascertaining the constancy of cardiac ejection velocity under various physiologic conditions in man.

1. *Stroke Volume Calculated From High-frequency Ballistocardiograms.*— In 1933 Abramson[6] reported on the design and construction of an extreme high-frequency (75 cycles per second with 70 kg. dead weight) chair ballisto-

*Jones has recently submitted for publication a paper in which criteria of normality were set up based on certain time intervals and a force measurement.[119]

cardiograph. The records he obtained were similar to those from the present-day high-frequency beds. He developed a formula for calculating cardiac output by relating the second integral of the ballistic waves to stroke volume. Starr and associates[7] have shown that this formula is of doubtful validity and is extreme difficult to apply. There is no indication that Abramson ever actually used his method for calculating cardiac output or that he applied it to clinical or physiologic problems.

In the original publication Starr and associates[7] derived the form of the ballistic complex when stroke volume was known and an ejection curve assumed; how this was accomplished has already been briefly considered. With the same assumptions Starr reversed the process to calculate stroke volume from the ballistic complex. He derived two formulas, one relating stroke volume to the amplitude of the I and J waves, the other relating stroke volume to the area of the I and J waves. Of the two Starr believed the area formula to be more accurate but chose to employ the amplitude formula because of its simplicity. He compared cardiac output estimated from the ballistocardiogram with that by the ethyl iodide method and found a correlation which was surprisingly high in view of the theoretical nature of the formula and of the assumptions involved. The ballistocardiographic method correlated as well with the ethyl iodide method as the latter did with itself when duplicate determinations were made. In spite of the simplicity of the amplitude method, Starr later discarded it for the area method which has been used ever since. In this original study it was believed that stroke volume could be calculated from ballistocardiograms abnormal in form but experience made it evident that this is not possible. In 1940, Starr and Schroeder[33] set up limits of normality for cardiac output based on values obtained in a group of normal subjects of both sexes from 20 to 40 years of age. They found that the average cardiac index in this group (1.91) was comparable to, but slightly lower than, the figures reported by Grollman[45] and by Lewis[46] both using the acetylene method. These figures are all considerably smaller than those obtained more recently through the application of the Fick principle and cardiac catheterization.

In 1942 Cournand, Ranges, and Riley[47] studied cardiac output in a group of patients by means of almost simultaneous Fick and ballistocardiographic determinations. Both methods were found to be consistent within themselves but the Fick values were 18.5 per cent higher than the ballistocardiographic values. These authors questioned the use of the aortic cross-section figures (Bazett) in the Starr formula and by roentgenographic measurements (with Diodrast) showed that they were too small. When the directly measured cross-section areas were used in the Starr formula, the mean difference between the Fick and the ballistocardiograph values was reduced to only 3.5 per cent. Starr has since shown that the use of the figure for the aortic cross-section area in the formula is unnecessary and has replaced it with a constant.[48]

Tanner[49] has recently restudied the normal standards for cardiac output. He analyzed the results obtained through the use of acetylene, ethyl iodide, Fick catheterization, and ballistocardiographic (high- and low-frequency) methods. When the catheterization and ballistocardiographic figures were compared there

was a high correlation, which became even higher when corrected for attenuation (correction for the variability inherent in each method). The constant in the Starr formula (high frequency) was adjusted to bring the absolute ballistocardiographic values into line with Cournand and associates'[50] catheterization values. The new formula, now in general use, is:

$$\text{Stroke volume} = 100\sqrt{(\text{Area } 2I + J)}\quad\sqrt{C}$$

where C represents cycle length in seconds. Tanner then set up limits of normality for stroke volume and cardiac output based on the findings in both men and women. He employed multiple regression equations rather than ratio standards.

REGRESSION EQUATIONS FOR STROKE VOLUME

Men:	S.V. = 25 S.A. − 0.5 heart rate −0.8 age + 103 Standard error of estimate = 11 c.c.
Women:	S.V. = 25 S.A. −0.2 heart rate −0.4 age + 56 Standard error of estimate = 7.5 c.c.

REGRESSION EQUATIONS FOR CARDIAC OUTPUT

Men:	C.O. = 1.1 S.A. − 0.05 age + 5.5 Standard error of estimate = 0.87 L./min.
Women:	C.O. = 1.7 S.A. − 0.04 age + 3.5 Standard error of estimate = 0.71 L./min.

It should be pointed out that different high-frequency ballistocardiograph beds may yield different mean I-J amplitude values in normal subjects in spite of a standard calibration procedure.[26] As Tanner advised, it is desirable to correct these equations on the basis of mean values for stroke volume, surface area, pulse rate, and cardiac output determined in each separate laboratory. The modified Starr stroke volume formula should not be applied when ballistocardiographic form is abnormal, nor can it be applied to the ballistocardiograms of patients in shock, for there is evidence that stroke volume calculated from the ballistocardiogram is abnormally high in this condition.[51]

Paine and Shock[52] studied the variability of ballistocardiographic cardiac output estimations with particular reference to the effect of meals, test-retest reliability, and errors of measurement. Galdston and Steele[53] made a critical study of cardiac output as determined by ballistocardiographic amplitude and area formulas. Taylor and Tiede[54] recently compared the results of various methods of estimating cardiac output (including high- and low-frequency ballistocardiographs) in relation to body size. They found that the high-frequency ballistocardiograph gives estimates of cardiac output which are unrelated to body size and believe it is therefore an unsatisfactory method. They also found that the use of cardiac index, rather than regressions, introduced so small an error as to be negligible.

2. *Stroke Volume Calculated From Low-frequency Ballistocardiograms.*—Henderson,[2] who used a type of low-frequency undamped bed, set up a simple formula for the estimation of relative cardiac output. He reasoned that the weight of the body (W) multiplied by the distance through which it is moved (D) must equal the weight of the blood ejected (w) multiplied by the distance through which it moves (d). He believed that the latter (d) was related to the height of the subject and so substituted height, "h," for "d." The equation then became $\frac{w}{W} = \frac{D}{h}$ and this simply states that the amount of blood ejected per unit body weight is equal to ballistic amplitude corrected for the height of the individual.

In 1945, Nickerson[55] reported the results of an extensive study of the physical properties of ballistic systems and developed a general theoretical approach to the estimation of stroke volume from the ballistocardiographic pattern. The formula for stroke volume he evolved and the one which is in current use is:

$$S.V. = \frac{5.02\ F \times P}{T \times L}$$

where F = force measured from the I-J amplitude of the ballistocardiogram; T = time duration between the peaks of the I and J waves; P = a blood-pressure factor which (over the usual range of pressures) is equal to the square root of the arithmetic mean of the systolic and diastolic pressures, and L = height of the subject in centimeters. The constant 5.02 was chosen to adjust the ballistic results to a best fit with the catheter data. Unlike Starr's formula, the Nickerson formula includes a factor (P) for estimating systolic ejection velocity and its use is based on the assumption that, since the blood must be ejected into the aortic tree against an average resistance proportional to the average systolic pressure, then its velocity will vary inversely with the average systolic pressure.

Nickerson, Warren, and Brannon[56] determined cardiac output by catheterization and almost simultaneous ballistocardiographic measurements in a group of subjects without heart disease. The fifty-four determinations on these thirty-two subjects showed good agreement between the two methods. Eighty-seven per cent of the ballistocardiographic values fell within ∓ 25 per cent of those by the catheter method. The correlation between the two ($r = 0.83$) was further improved ($r = 0.95$) by correction for attenuation.[49] The same good agreement was noted in studies on five patients in shock before and during treatment with saline and albumin. The agreement of the two methods was not as good in twenty-seven determinations on twenty-six patients with heart disease or myxedema. Excluding patients with aortic insufficiency, 60 per cent of the ballistic values of these patients fell within ± 25 per cent of the catheter values. Considering all subjects, whether with or without heart disease, it was found that variation in arterial blood pressure, heart rate, and age seemed to cause no significant variation in the relationship of cardiac output as measured by the catheterization and ballistocardiographic methods.

Winchell and associates[57] have recently determined cardiac output in a group of subjects by both acetylene and low-frequency ballistocardiographic techniques. They found that the relationship between the two methods did not change over a wide range of blood pressures, results similar to Nickerson's. In the study by Taylor and Tiede,[54] referred to above, the low-frequency ballistocardiograph, unlike the high-frequency bed, yielded cardiac output values which were related to body size. Gregerson and Nickerson[58] found that cardiac output (low-frequency bed) shows a definite relationship to body type as well as to body size.

The most serious objections to the use of the ballistocardiograph in estimating cardiac output have been raised by Hamilton and associates.[19] They believe that individual variation in ejection velocity curves in normal persons may greatly modify the relationship between stroke volume and the ballistocardiographic forces and thereby lead to large, unpredictable errors. It was shown that with the same stroke volume different ejection curves produce different calculated ballistic forces and therefore different ballistocardiographic stroke volumes. However, their results were based for the most part on calculations of ballistocardiographic forces from cardiac ejection curves which were in turn calculated from pressure pulse contours recorded from the brachial artery. More recently, Remington, Noback, Hamilton, and Gold[59] have come to the conclusion that the brachial pulse tracing cannot be used to calculate ejection curves because of the changes in pulse contour in its passage through the arterial bed. It would therefore appear that the previous calculations of ballistocardiographic forces from the ejection curves constructed in this manner are inapplicable. There is little doubt that differences in ejection velocity produce differences in recorded ballistocardiographic forces, but the normal variation in cardiac ejection curves from one person to the next is not known at present. That these differences are not excessively large is suggested by the fact that the scatter of ballistocardiographic cardiac output values is no greater than that of other cardiac output methods,[33,49] and the additional evidence that the ballistocardiographic method correlates well with the other methods of determining cardiac output.[7,47,56] There is still a need for comparative cardiac output studies using the ballistocardiographic and Fick or dye dilution methods in a group of subjects under changing physiologic conditions in order to discover whether the two methods correlate well under the circumstances encountered in clinical cardiovascular studies.

The advantages of the ballistocardiographic method of determining cardiac output are important ones. It is a simple, rapid method and one which causes the patient no discomfort or anxiety. It allows the study of rapid circulatory changes and is the only method providing an estimate of stroke volume for individual heart beats. It cannot be used when ballistic form is abnormal nor is it applicable in patients with moderate or severe dyspnea, marked tremor, or with arrhythmias of certain types.

F. RESPIRATORY VARIATION IN THE BALLISTOCARDIOGRAM

Normal ballistocardiograms show variation in the size of the ballistic complexes during the respiratory cycle. In 1946 Starr and Freidland[60] reported the results of a study on the causes of this respiratory variation. They showed that the phase and magnitude of the ballistic respiratory variation are dependent on the changes in intrathoracic pressure and not on changes in cardiac position during breathing. It was pointed out that whereas arterial systolic and pulse pressures increase during expiration, suggesting an increase in cardiac output, the ballistocardiographic complexes are smallest during expiration, suggesting a decrease in cardiac output during this phase of respiration. Their studies suggested that during expiration the output of the left ventricle increases while at the same time the output of the right ventricle and of the heart as a whole decreases; during inspiration the reverse is believed to occur. Since the ballistocardiogram reflects changes in the output of the heart as a whole, its amplitude increases during inspiration and decreases during expiration. This concept is in accord with the results of earlier work by Boyd and Patras[61] and Schuler and associates[62] who studied the differential effects of respiration on the right and left ventricles, and by Lauson and associates,[63] who inferred, from pulmonary and systemic arterial pressure tracings, changes in the output of the two ventricles during respiration. Williams and Gropper[64] have recently supplied additional evidence by combining the ballistocardiographic and the Remington pressure pulse[59] methods to estimate total cardiac output and left ventricular output, respectively. They found that the variation in right ventricular output during breathing is several times as large as that of left ventricular output, a finding previously documented by Lauson and associates[63] using another method.

Changes in the rate, depth, and character of respiration may cause changes in the respiratory variation of the ballistocardiogram. There is also evidence that other nonrespiratory factors also influence ballistic respiratory variation. Brown and associates[35,44,65] have noted increased respiratory variation in patients with angina pectoris and hypertension and in subjects following sympathectomy. They suggest that increased respiratory variation may be due to a diminished "pulmonary blood pool" which in turn may result from peripheral and splanchnic blood pooling. In a patient previously subjected to a bilateral sympathectomy the application of an abdominal binder and elastic stockings, which presumably reduced the peripheral and splanchnic pools, caused a distinct decrease in the respiratory variation of the ballistocardiogram. They also found that there was a reduction of respiratory variation and an improvement in the form of ballistocardiograms from certain patients with angina pectoris who were allowed to wear abdominal binders.[66]

III. Clinical Application of Ballistocardiography

The ballistocardiograph has been applied in clinical and laboratory investigation to a wide variety of problems. It is beyond the scope of this communication to discuss in detail all of the applications which have been documented, but nevertheless an attempt will be made to outline some of the more important uses

of the method. It should be kept clearly in mind that the work to be quoted was carried out with instruments which varied widely in type and that the criteria for normality of the records have varied considerably from worker to worker.

A. CARDIAC OUTPUT STUDIES

Of all the clinical and laboratory purposes to which it has been applied, the ballistocardiograph has probably been most often utilized in an effort to estimate cardiac output. The methods by which this is accomplished, and an appraisal of their validity have been previously considered (Section II. E. *Determination of Cardiac Output*). In this discussion the fields of application will be outlined and unless otherwise indicated the term cardiac output will refer to that estimated with the ballistocardiograph. Since the early studies, the formulas for the calculation of cardiac output have undergone a number of evolutional changes; therefore, absolute values for output are less significant than relative ones.

The earliest application of this means of determining cardiac output was by Douglas and associates[67] in the Anglo-American Pike's Peak studies. Cardiac output was believed to be only slightly increased at high altitude. Since his development of the ballistocardiograph as a means of estimating cardiac output,[7] Starr has applied the method to a wide variety of clinical problems. Early in the course of his work he was impressed with the low and high outputs of certain individuals without apparent organic disease, for example, neurocirculatory asthenia, and termed these phenomena "hypo- and hyperkinemia," respectively.[68-71] At approximately the same time he reported on the changes in cardiac output in response to arising from the supine to the erect position and hypothesized that deviation from the "normal" response resulted from "incoordination of the circulation."[72] In 1945 he applied this method of observation to surgical convalescent patients, and demonstrated both a postoperative fall in output, and a delay in return of cardiac output to control levels following mild exercise.[73,74] In contrast, Fleming and associates[75] have recently reported an early increase in cardiac output, as determined with the low-frequency bed, in postoperative patients.

The changes in cardiac output with various other physiologic influences have been investigated. Paine and Shock[52] studied the effect of the ingestion of a standard meal in normal individuals and found that cardiac output rose almost immediately to a peak of 12 per cent and remained elevated for approximately five and one-half hours. Berman and associates[76] also showed an increase in cardiac output (mean of 24 per cent) in normal subjects studied thirty minutes after a standard meal; in contrast a slight reduction in cardiac output was found in a small group of patients with coronary artery disease.

The inhalation of 100 per cent oxygen has been shown to decrease cardiac output slightly.[77-80] On the other hand, anoxemia was found to increase cardiac output,[80-82] the increase being roughly proportional to the degree of arterial desaturation. Similar changes in cardiac output have been found under conditions simulating high altitude.[81-83] The effect of exercise on cardiac output has been studied by a number of observers including Starr, Mayock, and Battles,[73,74] Makinson,[84] Mathers and associates,[85] and Stevenson and associates.[86] There

is general agreement that cardiac output rises in normal subjects following exercise but there is considerable individual variation in response. Stevenson and associates[86] and Hickam and associates[87] showed that anxiety increases cardiac output and produces an effect similar to that of moderate activity.

Following the intravenous administration of isotonic fluids Hardy and Godfrey[88] found little effect in normal individuals but a marked increase in cardiac output in subjects who were dehydrated. Segers and Walsh[89] noted an increase in cardiac output of 10 to 30 per cent following the administration of hypertonic glucose to normal persons and patients with cardiac dysfunction, but the increase was more sustained in the latter group. A rise in cardiac output after intravenous gelatin was noted by Fletcher and associates.[90]

The ballistocardiograph has been utilized by several groups to study the acute effects of drugs. Wilkins and Duncan[91] noted a fall in cardiac output after the administration of angiotonin, a finding which was confirmed by Taylor and Page[92] who also observed a similar decrease after tyramine and guanidine. Eichna and associates[93] studied the acute effects of intravenous cardiac glycosides on subjects without heart disease; there was a slight decrease in cardiac output due to a decrease in pulse rate. Kaufman and associates[94] found no change in cardiac output with Priscoline (2-benzyl-4,5-amidazoline hydrochloride) and Winchell and associates[57] found a decrease after oral Sodoum Amytal. Wegria and associates,[95] using the low-frequency bed, found an increase in stroke volume and in cardiac output following sublingual nitroglycerin. Brandt and associates[96] noted an increase in the amplitude of electromagnetic ballistocardiograms following nitroglycerin; simultaneously recorded roentgenkymograms revealed a slight decrease in estimated stroke volume but an increase in minute volume. Starr and Rawson[21] found that Paredrine [p(2-aminopropyl) phenol H cl.] diminishes stroke volume when the subject is recumbent but increases it when he is erect. Barcroft and Starr[97] studied the effects of intravenous infusions of Adrenalin and noradrenalin and found that, while both increase blood pressure, Adrenalin increases cardiac output (+40 per cent) whereas noradrenalin reduces it(−32 per cent). Levy and associates[98] studied changes in cardiac output (low-frequency bed) produced by smoking cigarettes. There was a slight fall (1.8 per cent) in normal subjects and a slight rise (6.4 per cent) in patients with heart disease.

The influence of respiratory factors on cardiac output has been studied by several workers. Otis, Cain, and others[77,99] found a reduction in stroke volume in subjects who breathed against continuously elevated pulmonary pressure; the same result was noted when pulmonary pressure was elevated during the inspiratory phase alone. They also found a slight reduction in cardiac output during voluntary hyperventilation but no consistent change when pulmonary dead space was increased. Brown, de Lalla, and Hoffman[35,44,65] have called particular attention to the variation in stroke volume during respiration and they believe that increased respiratory variation may be an early manifestation of cardiovascular dysfunction. These authors devised a "respiratory variation index" (R.V.I.) which is calculated by the following formula: R.V.I. = Inspiratory cardiac output − Expiratory cardiac output (in c.c./min.) ÷ surface area (in square meters). High values for this index were found in patients with

angina pectoris whereas there were low values in normal subjects. A number of observers have found that the first trend toward abnormality in a ballistocardiogram is reduction in the size of the complexes during expiration. It is not known whether this actually represents a decrease in stroke volume during expiration or a decrease in ejection velocity with a normal stroke volume.

The question as to whether the ballistocardiograph may be used with assurance as a means of studying changes in cardiac output under varying physiologic conditions cannot be fully answered at this time. The method is at its best when it is used to estimate changes in output in the same individual during acute experiments but there is as yet insufficient evidence that this method correlates as well with other methods during such acute experiments as it does under resting conditions.

B. THE BALLISTOCARDIOGRAM IN CLINICALLY NORMAL PERSONS

Before a new diagnostic instrument, such as the ballistocardiograph, can be properly applied to clinical cardiovascular problems its performance should be studied extensively in clinically normal subjects. Unfortunately, the results of large studies have become available only recently. There appears to be general agreement that clinically normal persons below the age of 35 or 40 years who have no condition known to affect the heart and circulation almost invariably (if not always) have normal ballistocardiograms. The first suggestion that the ballistocardiogram is not always normal in healthy persons of *all* ages was made by Starr[100] when he reported ballistocardiographic studies on ninety normal subjects above the age of 40 years. Only four of the ninety (4.4 per cent) had abnormal records. In the last two years several studies have been reported indicating a much higher incidence of abnormal records in older normal subjects. These results are not strictly comparable because postexercise records were often included in the form evaluation and because there were differences in the methods of classification. Dock, Mandelbaum, and Mandelbaum,[37,101,102] using the direct-body ballistocardiograph, studied a large number of normal subjects over a wide age range before and after exercise. They found no abnormal resting ballistocardiograms in subjects under 40 years of age but an increasing frequency of abnormality in the older age groups. In the seventh decade only 25 per cent of the subjects had normal records both before and after exercise.

Pordy and associates[103] and later Taymor and associates,[104] using the photoelectric pickup, carried out similar studies with comparable results. Their ballistocardiograms were graded "normal," "borderline," and "abnormal." Pordy found that 93 per cent of the normal subjects below the age of 50 had normal records whereas above 50 this incidence was 81 per cent. In Taymor's more recent study, it was found that, among subjects with a negative Master test, in those below the age of 50 there were abnormal ballistocardiograms (before or after exercise) in 13 per cent, but in those above the age of 50 the records were abnormal in 37 per cent. Gubner[105] also used the photoelectric pickup in the study of normal subjects and found that important changes were frequent in the ballistocardiograms from older normal persons. Among these changes were increased respiratory variation, relatively tall H waves, short I waves, low slurred J waves, deep and early K waves, and tall L waves.

Scarborough and associates[16] recently studied 369 clinically normal persons and also found a high incidence of ballistic abnormality in those above the age of 50. There were no abnormal records in subjects below 40 but thereafter the incidence rose precipitously to a peak of 92 per cent in the eighth decade. Below the age of 50, abnormal records were present in only 4 per cent of 214 subjects whereas above the age of 50 there were abnormal records in 55 per cent of the 155 subjects.

The similarity between the increasing incidence of ballistocardiographic abnormality and the increasing incidence of coronary sclerosis with age[106] suggests, but does not establish, a relationship between these two findings. The exact causes of the ballistocardiographic abnormality in older normal persons remains to be proved.

Although no precise criteria of normality for the ballistocardiogram have been agreed on, limits of normality have been defined for amplitude, duration, and certain other variables for both high- and low-frequency ballistocardiograms.[16,17,29,107] It is suggested that the reader refer to the original reports for details.

C. CORONARY ARTERY DISEASE

Since its recent introduction to clinical medicine, the ballistocardiograph has been utilized with increasing frequency in the evaluation of patients with coronary artery disease. Great hope has been expressed that this instrument would provide a more sensitive method for the detection of cardiac dysfunction resulting from ischemic myocardial changes both in patients with cardiac symptoms and in subjects without demonstrable evidence of cardiovascular disease. There is also the hope that the ballistocardiograph will be of value in predicting the future course of the individual patient with coronary artery disease. A review of the literature with respect to the use of ballistocardiographic techniques in coronary artery disease has recently been reported and the findings in 326 patients with angina pectoris or old myocardial infarction were described.[108]

Early in his clinical studies Starr[33] noted that the three specific types of abnormal ballistic complexes (early M, late M, and late downstroke) were all found in the records of patients with coronary sclerosis. In 1943 Starr and Wood[109] reported that 26 per cent of patients with myocardial infarction and 15 per cent of those with angina pectoris had abnormal ballistocardiograms. That this incidence of form abnormality was unduly low is suggested by a more recent summary by Starr and Mayock[110] which indicated that 50 per cent of their 127 cases of coronary disease had abnormal records. Starr[111] has suggested that among the patients who have survived a myocardial infarction those whose ballistocardiograms remain normal have a more hopeful prognosis. However, there is not yet sufficient data to warrant final conclusions with regard to the prognostic value of the ballistocardiogram in such patients. A very significant contribution was made by Starr[100] in 1947 when he reported the results of a long-range clinical follow-up on ninety clinically normal persons studied with the ballistocardiograph. Four of them had abnormal records and, during the following eight to ten years, three developed manifest coronary artery disease. In addition, twelve subjects whose original records were unusually small also de-

veloped either angina pectoris or myocardial infarction. These results suggest a correlation between ballistic abnormality and coronary atherosclerosis in subjects free of cardiac symptoms. There has been no confirmation of these findings by other investigators as yet. Starr and Hildreth[107] have recently reported another follow-up study on eighty subjects who were healthy when originally studied 10 to 14 years before. The ballistocardiograms were correlated with the clinical course. In addition, the change in ballistic form due to aging was determined from the records of those subjects who remained healthy during the follow-up period.

The incidence of ballistocardiographic abnormality in patients with coronary artery disease published by Starr is considerably lower than that reported by others using the high-frequency bed. The reasons for this discrepancy are not clear. Berman and associates[76] reported that 78 per cent of a group of patients with angina pectoris had abnormal records, and Brown and associates[44] found some degree of abnormality in all of twenty-six patients with this condition. Scarborough and associates[108] found the over-all incidence of abnormal ballistocardiograms to be 74 per cent among patients with angina pectoris or old myocardial infarction. However, there was a distinct age trend. Only 40 per cent of patients in the fourth decade, but 100 per cent of those in the eighth decade, had abnormal records.

In the study by Brown and associates[44] there appeared to be a relationship between the degree of ballistic abnormality and the severity of the disease in their patients with angina pectoris. They called attention to the presence of increased respiratory variation among the patients and devised an index for expressing the magnitude of the respiratory variation. Through the use of this index they were able (almost completely) to separate patients with angina pectoris from normal control subjects. However, others[15,108] have not been able to confirm these results and have found this index to be highly variable. Brown noted that abdominal compression produces marked improvement in the ballistocardiograms of some patients with angina pectoris. A group of such patients was selected to wear abdominal binders for an eighteen-month period; there was a definite reduction in symptoms and an increase in exercise tolerance in a high proportion of them.[66] De Lalla and Brown[65] suggest that in certain cases coronary insufficiency may be secondary to a critically low left ventricular output caused by splanchnic pooling and that by using abdominal binders pooling may be decreased and left ventricular output increased. Improvement in the ballistocardiograms from patients with coronary artery disease subjected to abdominal compression was also observed by Scarborough and associates.[108] These workers noted similar improvement in abnormal records from older normal persons after the same procedure.[16]

Makinson,[84] using the high-frequency bed, studied a group of patients with angina pectoris before and after standard exercise. There was an increase in cardiac output after exercise which was quite similar in magnitude to that in a group of normal subjects. In at least one of the patients a normal resting ballistocardiogram became abnormal after exercise. The production of form abnormality by exercise has been noted by others (see below). The effect of another type of

stress, anoxemia, on patients with coronary artery disease and on normal subjects has been studied.[80] The results revealed a comparable increase in cardiac output in both groups but, among the nine patients with angina pectoris, the ballistocardiograms of four became abnormal or more abnormal during anoxemia. Berman and associates[76] found an insignificant change in cardiac output (−4 per cent) in patients with angina pectoris following the ingestion of a standard meal whereas in normal subjects there was a considerable increase (+25 per cent). The response of patients with coronary artery disease to this type of "stress" therefore appears to be different from that produced by the physical stresses, exercise, and anoxemia.

Scott and associates[112] studied the effects of the parenteral administration of khellin on the ballistocardiograms of eight patients with angina pectoris. Four of them had abnormal control ballistocardiograms and these did not change after the injection of the drug. In the remaining four, with normal control ballistocardiograms, there was a slight increase in cardiac output in one and a decrease in three.

Few reports are available concerning the use of the low-frequency ballistocardiograph in the study of patients with coronary artery disease. Mathers, Nickerson, and others[113] studied four patients with coronary sclerosis, three of whom showed abnormal patterns which improved with digitalization. In another study, Mathers and associates[85] contrasted the cardiovascular responses of five normal persons and five patients with coronary artery disease to ascending a flight of ordinary stairs and found similar results in both groups.

Extensive studies of patients with coronary sclerosis have been made with Dock-type direct-body ballistocardiographs. Dock and Taubman[9] observed that men under the age of 35 years who have recovered from myocardial infarction may show normal ballistocardiograms. Several studies by Dock, Mandelbaum, and Mandelbaum[37,101,102] have demonstrated a high incidence of ballistic abnormality in patients with coronary artery disease. Normal records at rest were found in only 11 per cent of 224 patients with angina pectoris, and after exercise this decreased to less than 1 per cent. The frequency of ballistic abnormality among their patients showed a distinct age trend, abnormal records being more frequent among the older persons.[37] This finding is similar to that noted by others using a high-frequency bed.[108]

Large groups of patients have also been studied by Taymor, Pordy, and others[103,104] using the photoelectric direct-body pickup. These investigators compared ballistocardiographic form (pre- and postexercise) with the electrocardiographic response to the Master "two-step" exercise test. Of patients with positive Master tests, the resting ballistocardiogram was abnormal in 83 per cent before exercise and in 93 per cent after exercise. On the other hand among those with negative Master tests the ballistocardiogram was abnormal in only 16 per cent before exercise and in 24 per cent after exercise. The correlation between the results of the ballistocardiographic and electrocardiographic (with Master test) studies was good but not perfect inasmuch as the two supply information about different cardiac functions. Gubner[105] has also reported on ballistocardiographic abnormalities (direct-body pickup) in patients with coronary sclerosis.

A deterioration of ballistocardiographic form after smoking cigarettes has been noted in the direct-body pickup records from patients with coronary artery disease as well as in those from some normal subjects.[114,115] Mandelbaum and Mandelbaum[115] suggest the use of the ballistocardiograph for determining nicotine sensitivity and believe that tobacco should be banned in those cardiac patients who show a positive "cigarette test."

The practical diagnostic values of ballistocardiography in the study of patients with coronary artery disease is still somewhat uncertain. The bulk of evidence indicates that an abnormal ballistocardiogram may be expected in a high proportion of patients with symptomatic coronary disease. However, the high incidence of *normal* records in young patients with coronary disease and the high incidence of *abnormal* records in older clinically normal persons necessarily makes for caution in clinical interpretation. The use of stress tests in conjunction with ballistocardiography may be of considerable value, but it should be pointed out that, while exercise increases the incidence of abnormal records in patients with coronary disease, it also increases it in normal subjects as well.

It may be argued that the ballistocardiographic abnormality encountered in older normal persons is produced by "subclinical" coronary artery disease. Only a long-term follow-up program can confirm or deny this argument.

D. OTHER CARDIOVASCULAR DISORDERS

The ballistocardiograph has been applied to the study of a wide variety of cardiovascular disease entities in order to define its limits of clinical utility and to evaluate the specificity of its information. These investigations are still in progress and, therefore, no final conclusions are justified. However, the accumulated data allow certain preliminary generalizations regarding the specificity of the method. Attempts to delineate ballistocardiographic patterns which are diagnostic of specific cardiovascular disease states have been largely unsuccessful. This is due, in the main, to the fact that the ballistocardiograph tends to reduce all varieties of anatomic abnormality to the common physiologic denominator of mechanical force. However, certain pathologic conditions do cause characteristic physiologic alterations and these may produce characteristic ballistocardiograms.

The effects of *hypertension* on the ballistocardiogram have been extensively studied. In general terms, "ballistocardiographic life history" can be reconstructed. The majority of the patients in the early stages of the disease have normal ballistocardiograms. As the disease progresses, there is a tendency for a deep K wave to appear. The deep K is often associated with increased respiratory variation in amplitude and in some instances with decreased cardiac output. These changes have been found with the three major varieties of ballistocardiographic technique.[17,34,37,64,101] Other abnormalities may then appear, including short to absent I wave, notched or deformed J, and as further progress of the disease occurs, there may be marked abnormality, such as "early M's," "late downstrokes," or completely bizarre complexes. Temporary reversal of the abnormal pattern, and in some cases reversion to normal form, has been obtained with hexamethonium and other sympatholytic agents.[26]

In contrast to the deep K wave of hypertension, short K waves have been noted in *aortic stenosis*[116] and in *hypotension*.[35,37] In addition, short or absent K waves have consistently been noted in *coarctation of the aorta*. The dynamic relationship of the K wave to aortic length, and the predicted and actual shortening of the K with high aortic obstruction were demonstrated by Hamilton and associates[10] and Nickerson and associates.[30,38] Perhaps the most striking demonstration of the absent K wave pattern in the presence of this lesion has been made by groups utilizing the low-frequency bed, with which practically all cases have been found to show the "classical" pattern.[17,30,38,39] In these records the IJ is usually tall, the K small or absent, and delayed.[17] Similar findings have been reported with the high-frequency bed.[36] In either case a more normal K wave appears in the postoperative record in the great majority of instances, if adequate end-to-end aortic anastomosis is established. Improved but less striking records have been found after subclavian-aortic anastomosis.[30,39] It is of interest that thrombosis of the abdominal aorta has been reported to produce similar ballistocardiographic findings.[39,40]

Studies on patients with *rheumatic heart disease* have been far from complete. Starr and Dock have mentioned abnormal form in the presence of *acute carditis*, which improves with clinical remission.[9,37] In the presence of established *rheumatic valvulitis* abnormal form, generally nonspecific in nature, is often found. Starr and Mayock[110] report abnormality in 45 per cent of such cases, and both Starr[117] and Mathers and associates,[113] with high- and low-frequency beds, have commented on the improvement in form following digitalization. Abnormally tall and prolonged L waves have been noted in some cases of *mitral stenosis*.[37,116] Others[118] have been struck with abnormality of the early portion of the systolic complex (slurred, doubled, or otherwise deformed I waves). After experimentally inducing *mitral insufficiency* in dogs, Newman and associates[119] found no definite change in the ballistic pattern from the low-frequency bed.

Aortic insufficiency, whether of rheumatic or syphilitic etiology, usually produces abnormally large complexes with short I waves and deep K waves.[17,30,34] Calculated cardiac output is higher than usual because total rather than "effective" output is measured with the ballistocardiograph.[30,56] However, the onset of congestive heart failure may be associated with decreased amplitude and bizarre complexes.

Inordinately large ballistic complexes are frequently found in patients with those varieties of cardiovascular disease which are of the "high output" type. Such findings have been reported in *arteriovenous fistulas*, *anemia*, *thyrotoxicosis*, *emaciation*, *patent ductus arteriosus*, and some forms of *pulmonary disease*.[30,34,37,68,117] These diseases are not always associated with high-amplitude ballistocardiograms, but when present such patterns may revert to normal if the output is decreased, as in compression or removal of an atriovenous fistula or patent ductus.[30,117] *Myxedema* and other diseases associated with low output may produce diminution in the amplitude of the ballistocardiogram.

Congestive heart failure, regardless of its cause, is usually associated with ballistic form abnormality; this tends to improve with restitution of compensation. Large diastolic waves have been observed in association with *gallop rhythm*,[9,37,42,43] and these tend to disappear when the gallop disappears.[42]

Constrictive pericarditis almost invariably produces an abnormal ballistocardiogram. Scarborough and associates,[41] utilizing a high-frequency bed, reported pre- and postoperative studies on patients whose records showed unusually large diastolic waves (especially in the lateral "vector" projection) which tended to decrease or disappear following satisfactory pericardiectomy. Both Starr and Schroeder[33] and Nickerson[30] noted an increase in the amplitude of the systolic waves following operation. Brown and de Lalla[35] found an extremely bizarre pattern in a patient with tuberculous pericarditis and Starr and Mayock[110] reported that 33 per cent of the cases of pericarditis of all types have abnormal records.

Arrhythmias and *conduction defects* are frequently associated with abnormal ballistic form, not only because of the electrical disturbances, but often because of underlying myocardial disease. *Sinus arrhythmia* produces large complexes when diastole (and the filling phase) is long, and small ones when it is short.[60] *Premature contractions* usually elicit small, often distorted complexes. *Auricular fibrillation* produces considerable variation in the size and form of the complexes, and the H wave may be present or absent. In *complete heart block* atrial systolic complexes can often be clearly separated from those produced by the ventricles.[7,26,30,32] Starr[34] has noted that *bundle branch block* may be associated with small I, low J, and deep K waves, but other types of abnormal patterns are seen and normal records are not unusual.

Pulmonary disorders are recognized by most workers as capable of producing ballistocardiographic alteration, due both to changes in respiratory dynamics and to the later effects on myocardial function. *Emphysema* is frequently accompanied by considerable increase in respiratory variation and often by abnormal form. A grossly abnormal record from a patient with *cor pulmonale* has been seen to revert to normal following pneumoperitoneum.[25] Mathers and associates[113] noted improved form in three such cases after digitalization.

It is hoped that improved technique and better understanding of the genesis of the ballistocardiogram will make possible more specific correlation between abnormality of form and specific disease entities. It is apparent from the preceding comments that at the present time the great majority of alterations are nonspecific in character: Improved cardiovascular function (whether produced by digitalis, surgery, or other therapeutic measures) is usually reflected in improvement of ballistic form, and clinical applicability is often limited to such generalizations of purpose. Such suggestive patterns as the absent K wave in coarctation of the aorta are clinically useful but in this, as well as in all other forms of cardiovascular disease, the ballistocardiograph should only be considered an adjunct to more conventional diagnostic and prognostic methods.

IV. Conclusions

No one can foresee at this stage in its development the ultimate role of the ballistocardiograph in clinical and investigative medicine. The technique is still a relatively new one and many of the underlying physical and physiologic principles remain to be elucidated. It is evident, however, that the ballistocardiograph is an instrument of great sensitivity, capable of supplying a new and

different kind of information about the functional state of the circulatory system. It promises to satisfy a long-felt and pressing need for information more directly related to the mechanical pumping function of the heart.

Although the ballistocardiograph has been used extensively for the determination of cardiac output, further work remains to be carried out before the validity and reliability of the method can be established. In any event, it seems likely that its greatest value will be in the detection of nonvalvular heart disease, and in the evaluation and prognosis of patients with overt cardiovascular disease. Its clinical usefulness in the diagnosis of coronary artery disease is tempered somewhat by the high frequency of abnormal records found in persons above the age of 50 years in whom there is no demonstrable evidence of cardiovascular disease. The causes of ballistic form abnormality in these "apparently normal" persons remains to be determined and until such time as it can be proved that this abnormality is a result of "subclinical" coronary artery disease great caution should be exercised in attributing clinical significance to abnormal records from older normal persons or from patients with symptoms atypical of coronary artery disease. Meanwhile, future investigation will be concerned with improvement and standardization of the instruments, further clinical exploration in specific cardiovascular disease states, and clarification of the physiologic import of ballistocardiographic form abnormality.

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